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peptide of influenza virus nucleoprotein (NP peptide) elicited

antigen-specific CTL responses as well as antibody

responses. In an in vitro cell depletion experiment, we demonstrated that the CTL activity against HBsAg elicited by EPI was attributed to CD8(+), not CD4(+), T cells. As controls, needle injections of HBsAg or the NP peptide into deeper tissues elicited solely antibody, not CTL, responses. We further demonstrated that EPI with inactivated A/Aichi/68 (H3N2) or A/Sydney/97 (H3N2) influenza virus elicited complete protection against a mouse-adapted A/Aichi/68 virus. In summary, EPI directly delivers protein antigens to the cytosol of the LCs in the skin and elicits both cellular and antibody responses.

- DUPLICATE 2 MEDLINE on STN ANSWER 2 OF 3 L6 Simian virus 40 large-T-antigen-specific PubMed ID: 11602701. 2001555951. rejection of mKSA tumor cells in BALB/c mice is critically dependent on both strictly tumor-associated, tumor-specific CD8(+) cytotoxic T lymphocytes and CD4(+) T helper cells. Utermohlen O; Schulze-Garg C; Warnecke G; Gugel R; Lohler J; Deppert W. (Heinrich-Pette-Institut fur Experimentelle Virologie und Immunologie an der Universitat Hamburg, D-20251 Hamburg, Germany.. olaf.utermoehlen@medizin.uni-koeln.de) . Journal of virology, (2001 Nov) 75 (22) 10593-602. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English. Protective immunity of BALB/c mice immunized with simian virus 40 (SV40) AΒ large T antigen (TAg) against SV40-transformed, TAg-expressing mKSA tumor cells is critically dependent on both CD8(+) and CD4(+) T lymphocytes. By depleting mice of T-cell subsets at different times before and after tumor challenge, we found that at all times, CD4(+) and CD8(+) cells both were equally important in establishing and maintaining a protective immune response. CD4(+) cells do not contribute to tumor eradication by directly lysing mKSA cells. However, CD4(+) lymphocytes provide help to CD8(+) cells to proliferate and to mature into fully active cytotoxic T lymphocytes (CTL). Depletion of CD4(+) cells by a single injection of CD4-specific monoclonal antibody at any time from directly before injection of the vaccinating antigen to up to 7 days after tumor challenge inhibited the generation of cytolytic CD8(+) lymphocytes. T helper cells in this system secrete the typical Th-1 cytokines interleukin 2 (IL-2) and gamma interferon. Because in this system TAg-specific CD8(+) cells secrete only minute amounts of IL-2, it appears that T helper cells provide these cytokines for CD8(+) T cells. Moreover, this helper effect of CD4(+) T cells in mKSA tumor rejection in BALB/c mice does not simply improve the activity of TAg-specific CD8(+) CTL but actually enables them to mature into cytolytic effector cells. Beyond this activity, the presence of T helper cells is necessary even in the late phase of tumor cell rejection in order to maintain protective immunity. However, despite the support of CD4(+) T helper cells, the tumor-specific CTL response is so weak that only at the site of tumor cell inoculation and not in the spleen or in the regional lymph nodes can TAg-specific CTL be detected.
- L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

  1999:64705 Document No. 130:138281 A method of inducing a CTL

  response. Kundig, Thomas M.; Simard, John J. L. (CTL

  Immunotherapies Corporation, Can.). PCT Int. Appl. WO 9902183 A2

  19990121, 199 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG,
  BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU,
  ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG,
  MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
  TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM;
  RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB,
  GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English).

  CODEN: PIXXD2. APPLICATION: WO 1998-US14289 19980710. PRIORITY: CA

  1997-2209815 19970710; US 1997-988320 19971210.
- AB A method of inducing a cytotoxic T-lymphocyte (CTL)
  response to an antigen is disclosed. The method involves
  delivering the antigen to the lymphatic system of an animal regularly over
  a sustained period of time using, e.g., an osmotic pump. The method is
  advantageous over prior art methods for inducing a CTL

response in that it does not require repetitive immunizations or the use of adjuvants. The method of the present invention can be used for the induction of CTLs in tumor or infectious disease immunotherapy.

=> s 12 and direct injection 101 L2 AND DIRECT INJECTION L7=> s 17 and lymph vessel 10 L7 AND LYMPH VESSEL => dup remove 18 PROCESSING COMPLETED FOR L8 9 DUP REMOVE L8 (1 DUPLICATE REMOVED) => d 19 1-9 cbib abs ANSWER 1 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN Document No. 136:289366 Use of VEGF as a lymphangiogenic agents 2002:276188 to treat lymphatic disorders. Gravereaux, Edwin C.; Silver, Marcy; Isner, Jeffrey M.; Yoon, Young-Sup (St. Elizabeth's Medical Center of Boston, Jeffrey M.; Yoon, Young-Sup (St. Elizabeth's Medical Center of Boston, Inc., USA). PCT Int. Appl. WO 2002029087 A2 20020411, 77 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR (English) CODEN: PIXXD2 APPLICATION: WO 2001-US30904 TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US30904 20011002. PRIORITY: US 2000-PV237171 20001002. The present invention provides methods for promoting the growth of new AΒ lymph vessels (lymphangiogenesis). Generally, such methods include administering at least one vascular endothelian factor (VEGF) such as VEGF-2. In one embodiment, therapeutic methods for treating lymphedema and related disorders in a human patient are disclosed. The VEGF can be provided by any suitable means including direct injection of a nucleic acid encoding same or an active fragment thereof. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new lymph vessel growth. Addnl., the rabbit VEGFR-3 cDNA and protein are both claimed. ANSWER 2 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN Document No. 137:320695 Use of VEGFs as lymphangiogenic agents 2002:794299 to treat lymphatic disorders. Gravereaux, Edwin C.; Silver, Marcy; Yoon, Young-sup; Isner, Jeffrey M.; Isner, Linda (St. Elizabeth's Medical Center of Boston, Inc., USA). U.S. Pat. Appl. Publ. US 2002151489 A1 20021017, 54 pp., Cont.-in-part of U. S. Provisional Ser. No. 237,171. (English). CODEN: USXXCO. APPLICATION: US 2001-970088 20011002. PRIORITY: US 2000-PV237171 20001002. The present invention provides methods for promoting the growth of new lymph vessels (lymphangiogenesis). Generally, such methods include administering at least one vascular endothelian factor (VEGF) such as VEGF-2. In one embodiment, therapeutic methods for treating lymphedema and related disorders in a human patient are disclosed. The VEGF can be provided by any suitable means including direct injection of a nucleic acid encoding same or an active fragment thereof. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new lymph vessel growth. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new

lymph vessel growth. Addnl., fragments of the rabbit

VEGFR-3 cDNA and protein are both claimed.

L9 ANSWER 3 OF 9 MEDLINE on STN
2001653877. PubMed ID: 11706493. [Lymphadenography--pioneering work of
Sven Bruun and Arnfinn Engeset]. Lymfadenografi--pionerarbeid av Sven
Bruun og Arnfinn Engeset. Kolbenstvedt A. (Radiologisk avdeling
Rikshospitalet 0027 Oslo.) Tidsskrift for den Norske laegeforening, (2001
Oct 10) 121 (24) 2836-7. Journal code: 0413423. ISSN: 0029-2001. Pub.
country: Norway. Language: Norwegian.

Lymphadenography is a method for direct radiologic visualization of lymph nodes following injection of fat soluble contrast medium. Sven Bruun and Arnfinn Engeset at Rogaland Hospital developed this method in 1952 and published preliminary results in 1956. They have been somewhat overshadowed by the English surgeon John B. Kinmonth who published his method on lymphangiography in 1954. Kinmonth succeeded in visualizing the peripheral lymph vessels by direct injection of water soluble contrast medium. By this technique it was not feasible to depict lymph nodes above the knee because of diffusion of medium to surrounding tissues. Lymphography is a technique that visualizes both lymph vessels and lymph nodes. This method is based on a combination of the two above-mentioned methods with injection of fat soluble contrast medium into peripheral lymph vessels. Lymphography was a very important examination which was used all over the world in the 1960s and 1970s. It has now been replaced by other examinations.

- L9 ANSWER 4 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 2000093020 EMBASE Lymphatic drainage of the heart and lungs in the pig: A preliminary study. Riquet M.; Hubsch J.P.; Chehab A.; Briere J.; Colomer S.; Hidden G.. Prof. M. Riquet, Laennec Hospital, Service de Chirurgie Thoracique, 42 rue de Sevres, 75007 Paris, France. riquet@lnc.ap-hop-paris.fr. European Journal of Lymphology and Related Problems 7/27 (80-84) 1999.

Refs: 17.
ISSN: 0778-5569. CODEN: EJLPE. Pub. Country: Belgium. Language: English.

Summary Language: English. In anatomy and physiology the pig is remarkably like man and is therefore AB considered as Potential Organ Donor. It was then particularly interesting to reconsider the lymphatic drainage of both its heart and lungs (H.L) Fifteen dead pigs were studied. The technique comprised removal of the sternocostal shield and injection into the myocardium and/or beneath the visceral pleura of a colored mass that was supplemented by direct injection of the nodes revealed in that manner. First colored nodes were tracheobronchial located-under the tracheal carina (ITBN), above the left (LSBN) and right (RSBN) main bronchus, above the right upper lobe tracheal bronchus (TBN) - and located at the lower level of the cervical trachea (CMN). There was no other pretracheal neither pulmonary LN contrary to human. The lymphatic vessels (LV) of the heart connected with the LSBN, rarely with the CMN. The LV issuing from : the ITBN connected with both the RSBN and LSBN and also with retrotracheal lymphcenter nodes (RTN); the RSBN connected with RTN, CMN or drained into the right jugulo subclavian venous confluent; The LSBN connected at times with RSBN and some lateroesophageal nodes, but generally drained into the left jugulosubclavian venous confluent, the arch of the thoracic duct (TD) and directly into the TD in the middle mediastinum, also an important lymph pathway in human. Lymphatics of the H.L. in pigs display anatomical patterns rarely observed in man but phylogeneticly explaining diseases as 'skipping' node metastases in lung cancer and chylothorax after heart and lungs surgery. In anatomy and physiology, the pig is remarkably like man. In 1966, Glauser underlined the advantages of Piglets as Experimental Animals in Pediatric Resarch : laboratory data comparing the newborn infant with the newborn piglet disclosed a striking similarity in the results reported for respiratory system. In adult research the pig's size proved to be a problem that was solved by breeding miniature pigs. Porcine coronary arteries have almost the same pattern as the human being and investigators have found the pig particularly valuable for the study of coronary arteriosclerosis. The similitude between the 2 species are so great and the differences so little that since recently pig is considered as a potential organ donor and most of its organs are thought suitable for xenotransplantation. In view of contributing to such major topics, it seemed particularly interesting to reconsider the lymphatic drainage of both heart and lungs in this species so closely related to human.

L9 ANSWER 5 OF 9 MEDLINE on STN
93143457. PubMed ID: 1843434. [Anatomy and topography of external iliac
lymph nodes in adults]. Anatomiia i topografiia
naruzhnykh podvzdoshnykh limfaticheskikh uzlov u vzroslogo cheloveka.
Shvetsov E V. Arkhiv anatomii, gistologii i embriologii, (1991 Jul-Aug)
100 (7-8) 50-7. Journal code: 0370603. ISSN: 0004-1947. Pub. country:
RUSSIA: Russian Federation. Language: Russian.

The investigation of the external iliac lymph nodes AB has been performed in 152 preparations of corpses of mature persons of both sex, who died from causes not connected with any disease of the lymphatic system, lower extremities and pelvic organs. The external iliac lymph nodes and their afferent and efferent lymphatic vessels have been revealed by means of interstitial injection of the lower extremities and pelvic organs, as well as by means of direct injection of Gerota mass into the lymphatic vessels. Form, amount, dimensions and topography of common iliac lymph nodes have been studied. Lymphatic vessels, running from certain parts and organs of the body to various subgroups of the external iliac lymph nodes have been described, as well as efferent lymph vessels of these nodes. The external iliac lymph nodes are constant formations; the largest of them--lymph nodes of the lacuna--are nodes of the I step for the lower extremity lymph vessels. In 54% of cases in persons of both sex positive (right-sided) asymmetry has been revealed. Total amount of the iliac lymph nodes prevails in men, while their size is greater in women. The size of these nodes in persons of both sex is greater to the left than to the right. There are connections (in 3% of cases) between the external iliac lymph nodes and aortal and lumbar nodes of the opposite

L9 ANSWER 6 OF 9 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 1993:339492 Document No.: PREV199396036492. Anatomy and topography of external iliac lymph nodes in adults. Shvetsov, E. V.. Div. Anat. Human, I.M. Sechenov Mosc. Med. Acad., Moscow, Russia. Arkhiv Anatomii Gistologii i Embriologii, (1991) Vol. 100, No. 6-8, pp. 50-57. CODEN: AAGEAA. ISSN: 0004-1947. Language: Russian.

AΒ

The investigation of the external iliac lymph nodes has been performed in 152 preparations of corpses of mature persons of both sex, who died from causes not connected with any disease of the lymphatic system, lower extremities and pelvic organs. The external iliac lymph nodes and their afferent and efferent lymphatic vessels have been revealed by means of interstitial injection of the lower extremities and pelvic organs, as well as by means of direct injection of Gerota mass into the lymphatic vessels. Form, amount, dimensions and topography of common iliac lymph nodes have been studied. Lymphatic vessels, running from certain parts and organs of the body to various subgroups of the external iliac lymph nodes have been described, as well as efferent lymph vessels of these nodes. The external iliac lymph nodes are constant formations; the largest of them lymph nodes of the lacuna - are nodes of the I step for the lower extremity lymph vessels. In 54% of cases in persons of both sex positive (right-sided) asymmetry has been revealed. Total amount of the iliac lymph nodes prevails in men, while their size is greater in women. The size of these

nodes in persons of both sex is greater to the left than to the right. There are connections (in 3% of cases) between the external iliac lymph nodes and aortal and lumbar nodes of the opposite side.

- ANSWER 7 OF 9 MEDLINE on STN [Anatomy and topography of the lymphatic PubMed ID: 6712496. 84178034. vessels and regional lymph nodes of the rectum in newborn infants and children to 3 years of age]. Anatomiia i topografiia limfaticheskikh sosudov i regionarnykh limfaticheskikh uzlov priamoi kishki u novorozhdennykh i detei do 3 let zhizni. Abdykerimov S A. Arkhiv anatomii, gistologii i embriologii, (1984 Feb) 86 (2) 65-9. Journal code: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language: Russian. In 30 corpses of newborns and children up to 3 years of age, by means of the intratissue and direct injection of the modified Gerota's mass, certain increase in number and size of the superficial inguinal lymph vessels belonging to the superior-medial group, as well as the pararectal and superior rectal lymph nodes has been noted. The diameter of both afferent and efferent lymphatic vessels in the nodes mentioned in children of 1-3 years of age is greater than in the newborns. The number of the afferent vessels running towards these nodes in most cases, regardless the age, prevail over the efferent ones, and the diameter of the latter is greater than in the afferent vessels. The pararectal lymph nodes in 80% of cases are the nodes of the first step for the lymph flowing from the rectum, in 15% - the nodes of the first and second steps, simultaneously, and in 5% - of the third and fourth steps. The superior pararectal lymph nodes in 80% of cases are the nodes of the third and fourth steps, and in 20% of cases - those of
- L9 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 1
  83021796. PubMed ID: 7125916. [Variants in the number and size and the topography of the lumbar lymph nodes in the regional of the liver in the human adult]. Varianty kolichestva, razmerov i topografiia regionarnykh dlia pecheni poiasnichnykh limfaticheskikh uzlov u vzroslogoo cheloveka. Usovich A K; Borziak E I. Arkhiv anatomii, gistologii i embriologii, (1982 Jul) 83 (7) 29-33. Journal code: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language: Russian.

the first and second steps for the lymph flowing from the rectum.

- By means of interstitial and direct injections of the AB lymphatic bed of the liver and gall bladder, their regional lymph nodes from the lumbar group have been studied in 63 corpses of mature persons of both sex. The hepatic lymph vessels flow into the lumbar lymph nodes in 73% of cases. Only the postaortal nodes (situating behind the abdominal part of the aorta) do not take the hepatic lymph nodes. The number of the hepatic regional lumbar lymph nodes varies from 1 to 6, and their size is within the limits 2X2--30X10 mm. Ιn 13% of cases intercalated lumbar lymph nodes have been revealed (6X4 mm in size), they are situated along the pathway of the visceral surface of the lymph vessels (of the right hepatic lobe) running towards large intermediate lumbar lymph nodes.
- L9 ANSWER 9 OF 9 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 74210138 EMBASE Document No.: 1974210138. [Lymph nodes and lymphatics of the pelvis and the pelvic limb of the goat]. DIE LYMPHKNOTEN UND LYMPHGEFASSE DES BECKENS UND DER BECKENGLIEDMASSE DER ZIEGE. Roos H.; Frewein J.. Inst. Makrosk. Anat. Tiere, Univ. Munchen, Germany. BERL.MUNCH.TIERARZTL.WSCHR. 87/6 (101-105) 1974. CODEN: BEMTAM. Language: German.
- The **lymph nodes** of the pelvis and the pelvic limb were examined in 46 goats of different breeds and different ages. Many of the afferent lymphatics were visualized by injection of a mixture of Indian

ink and water or Indian ink and serum into the subcutis, into fascias, tendons, tendon sheaths, joint capsules and ligaments. The efferent lymphatics were filled by direct injection into the lymph nodes. The following lymph nodes are always present: Ln. popliteus, Ln. ischiadicus, Ln. inguinalis superficialis, Ln. subiliacus, Lnn. iliaci mediales, and Ln. sacralis. Not always present are: Ln. tuberalis Ln. inguinalis profundus, and Ln. hypogastricus.

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L12 ANSWER 1 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004113784 EMBASE Optimised nuclear medicine method for tumour marking and sentinel node detection in occult primary breast lesions. De Cicco C.; Trifiro G.; Intra M.; Marotta G.; Ciprian A.; Frasson A.; Prisco G.; Luini A.; Viale G.; Paganelli G.. C. De Cicco, Division of Nuclear Medicine, European Institute of Oncology, University of Milan, Via Ripamonti, 435-20141 Milan, Italy. concetta.de-cicco@ieo.it. European Journal of Nuclear Medicine and Molecular Imaging 31/3 (349-354) Refs: 17.

ISSN: 1619-7070. CODEN: EJNMA6. Pub. Country: Germany. Language: English.

Summary Language: English.

The aim of this study was to evaluate the feasibility of sentinel node AB (SN) biopsy in occult breast lesions with different radiopharmaceuticals and to establish the optimal lymphoscintigraphic method to detect both occult lesions and SNs (SNOLL: sentinel node and occult lesion localisation). Two hundred and twenty-seven consecutive patients suspected to have clinically occult breast carcinoma were enrolled in the study. In addition to the radioguided occult lesion localisation (ROLL) procedure, using macroaggregates of technetium-99m labelled human serum albumin (MAA) injected directly into the lesion, lymphoscintigraphy was performed with nanocolloids (NC) injected in a peritumoral (group I) or a subdermal site (group II). In group III, a sole injection of NC was done into the lesion in order to perform both ROLL and SNOLL. Overall, axillary SNs were identified in 205 of the 227 patients (90.3%). In 12/62 (19.4%) patients of group I and 9/79 (11.4%) patients of group III, radioactive nodes were not visualised, whereas SNs were successfully localised in 85 of 86

patients of group II (P<0.001). Pathological findings revealed breast carcinoma in 148/227 patients (65.2%) and benign lesions in 79 (34.8%). A total of 131 axillary SNs were removed in 118 patients with breast carcinoma; intraoperative examination of the SNs revealed metastatic involvement in 16 out of 96 cases of invasive c arcinoma (16.7%). It is concluded that the combination of the ROLL procedure with **direct injection** of MAA into the lesion and lymphoscintigraphy performed with subdermal injection of radiocolloids represents the method of choice for accurate localisation of both non-palpable lesions and SNs.

- L12 ANSWER 2 OF 13 MEDLINE on STN DUPLICATE 1
  2002383730. PubMed ID: 12133274. Oncolytic herpesvirus effectively treats murine squamous cell carcinoma and spreads by natural lymphatics to treat sites of lymphatic metastases. Wong Richard J; Joe John K; Kim Se-Heon; Shah Jatin P; Horsburgh Brian; Fong Yuman. (Head and Neck Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.) Human gene therapy, (2002 Jul 1) 13 (10) 1213-23. Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English.
- Oncolytic herpesviruses have significant antitumoral effects in animal models when delivered directly to established tumors. Lymphatic metastases are a common occurrence for many tumor types. This study investigates the potential of an attenuated, replication-competent, oncolytic herpes simplex virus (NV1023) both to treat a primary tumor by direct injection and to travel through the lymphatic system to treat metastatic tumor within the lymph nodes draining lymph from the site of primary cancer. Isosulfan blue dye was injected into murine auricles to determine normal lymphatic drainage patterns and demonstrated consistent blue staining of a group of ipsilateral cervical lymph nodes. Auricular injections of NV1023 resulted in viral transit to these lymph nodes as measured by 5-bromo-4-chloro-3-indolyl-beta-D-galactopyranoside histochemistry and viral plaque assay. An oncolytic herpesvirus (NV1066) expressing green fluorescent protein also demonstrated viral transit from the auricle to the cervical lymph nodes on fluorescence microscopy. Using the SCC VII cell line, a novel murine model of auricular squamous cell carcinoma was developed with an approximately 20% incidence of cervical lymph node metastases. Delivery of NV1023 or NV1066 to the surgical beds after excision of auricular SCC VII tumors resulted in successful viral infection of metastatic SCC VII cells within the cervical lymph nodes. After a 7-week follow-up, significantly enhanced locoregional control (p < 0.05, Fisher exact test) and disease-free survival (p < 0.05, log rank test) were evident with NV1023 treatment. This study demonstrates that the delivery of an oncolytic herpesvirus to a primary tumor site after surgical excision may have a significant impact on reducing both primary site recurrence and regional nodal metastases.
- L12 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 2
  2002182449. PubMed ID: 11916241. Suppression of murine mammary carcinoma growth and metastasis by HSVtk/GCV gene therapy using in vivo electroporation. Shibata Masa-Aki; Morimoto Junji; Otsuki Yoshinori. (Department of Anatomy and Biology, Osaka Medical College, Takatsuki, Japan.) Cancer gene therapy, (2002 Jan) 9 (1) 16-27. Journal code: 9432230. ISSN: 0929-1903. Pub. country: England: United Kingdom. Language: English.
- The effectiveness of electroporation as a means of gene transfection, both in vitro and in vivo, was tested using the herpes simplex virus 1 thymidine kinase (HSVtk) gene in combination with ganciclovir (GCV) administration as therapy against murine mammary cancer. Approximately 80% of BJMC3879 metastatic mammary carcinoma cells, derived from MMTV-infected BALB/c mice, died as a result of HSVtk/GCV treatment 72 hours after the transfection; decreased DNA synthesis was also seen. Mammary tumors induced by inoculation of syngeneic mice with

BJMC3879 cells were subsequently treated by direct injection of vector containing HSVtk (pHSVtk) alone, empty vector or saline alone twice a week. After each injection, the tumors were subjected to in vivo electroporation. Mice treated with pHSVtk or saline were intraperitoneally injected with GCV at 40 mg/kg five times a week. Significantly reduced tumor volumes were observed for the pHSVtk+GCV group in experimental week 2 and thereafter throughout the 2-month study. DNA synthesis was significantly decreased as well in the pHSVtk+GCV group compared with all other groups. Furthermore, metastasis to lymph nodes and lungs was significantly suppressed by HSVtk/GCV treatment. Expression of HSVtk in the tumors was confirmed by RT-PCR. Macrophage accumulations were frequently observed in the peripheries of necrotic regions in HSVtk/GCV-treated tumors, where levels of apoptosis were significantly higher than those observed in other groups. We therefore conclude that in vivo electroporation can result in efficient gene transfer and that the HSVtk/GCV prodrug system strongly suppresses tumor growth and metastases in this model.

L12 ANSWER 4 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:625155 The Genuine Article (R) Number: 224AQ. Distribution of retroviral vectors and vector producer cells using two routes of administration in rats. Kaloss M; Linscott M; Wey C; Lu P; Long Z; McGarrity G J; Otto E; Lyons R M (Reprint). GENET THERAPY INC, 938 CLOPPER RD, GAITHERSBURG, MD 20878 (Reprint); GENET THERAPY INC, GAITHERSBURG, MD 20878. GENE THERAPY (AUG 1999) Vol. 6, No. 8, pp. 1389-1396. Publisher: STOCKTON PRESS. HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0969-7128. Pub. country: USA. Language: English.
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

The clinical use of retroviral vector producer cells (VPCs) to deliver retroviral vectors efficiently to target cells has been investigated as a method to increase efficiency of gene delivery, presumably as a result of continued vector production in vivo. Studies were conducted in rats to evaluate the distribution of vector to distal organs and tissues as measured by transduction. Rats were treated with two doses of VPCs using two routes of administration: (1) subcutaneous injection, chosen to maximize both the dose and exposure of animals, thereby enabling identification of potential target organs under worst-case conditions; and (2) direct injection into brain parenchyma, chosen to mimic the intended clinical route of administration and provide an estimate of risk to patients receiving this therapy. Twelve organs or tissues were collected 7 days after administration of VPCs and analyzed by PCR for the presence of vector and vector producer cell sequences. Vector was detected most frequently at the site of injection by either route of administration. Less frequently, vector was detected in draining lymph nodes at the higher dose only using either route of injection. Single specimens of lung and contralateral skin were positive for vector following subcutaneous administration only. Vector was detected in gonadal tissue from a single low-dose male following subcutaneous administration, but this finding was not reproduced in any high-dose male or any males injected intracerebrally. In contrast, VPCs were detected only at the site of administration. The frequency of detection of VPCs 7 days after administration was higher when rats were injected by the intracerebral route. Based on these studies, gene transfer to distal organs or gonadal tissue following intracerebral administration of VPCs is not considered to be a risk to patients undergoing retroviral Vector gene therapy for the treatment of brain cancer (glioblastoma multiforme; GBM).

L12 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 3
1998033894. PubMed ID: 9367025. Cytokines as an adjuvant to tumor
vaccines: efficacy of local methods of delivery. Kurane S; Arca M T; Aruga
A; Krinock R A; Krauss J C; Chang A E. (Division of Surgical Oncology,
University of Michigan, Ann Arbor, USA. ) Annals of surgical oncology:
official journal of the Society of Surgical Oncology, (1997 Oct-Nov) 4 (7)
579-85. Journal code: 9420840. ISSN: 1068-9265. Pub. country: United

States. Language: English. BACKGROUND: We examined alternative methods of delivering cytokines as an AΒ adjunct for priming lymph node (LN) cells draining sites of vaccine inoculation for the purpose of generating immune cells for adoptive immunotherapy. METHODS: Using syngeneic murine tumors we examined the ability of IL-2, IL-4, or GM-CSF delivered locally to a site of tumor inoculum to induce antitumor reactive draining LN cells. Mice were inoculated subcutaneously with tumor cells transduced to secrete cytokine; tumor cells admixed with fibroblasts transduced to secrete cytokine; or intralesional inoculation of cytokine in established tumor to induce sensitized LN cells capable of mediating tumor regression in adoptive transfer. RESULTS: Both IL-4 and GM-CSF cytokines were effective in enhancing the antitumor reactivity of vaccine-primed LN cells compared to IL-2, which was ineffective. The local delivery of GM-CSF by autocrine or paracrine secretion of genetically engineered cells, as well as direct intratumoral delivery was capable of upregulating LN sensitization compared to systemic administration, which did not. CONCLUSIONS: The local delivery of GM-CSF as an adjuvant for tumor vaccination can be accomplished by various methods, including direct injection, which avoids the need for gene transfer.

L12 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 4
97159158. PubMed ID: 9006499. A new immunocompetent murine model for oral
cancer. O'Malley B W Jr; Cope K A; Johnson C S; Schwartz M R. (Department
of Otolaryngology-Head and Neck Surgery, Johns Hopkins University,
Baltimore, Md, USA.) Archives of otolaryngology--head & neck surgery,
(1997 Jan) 123 (1) 20-4. Journal code: 8603209. ISSN: 0886-4470. Pub.
country: United States. Language: English.

OBJECTIVE: To develop and characterize a new immunocompetent murine model AΒ that attempts to parallel the clinical and biological nature of head and neck cancer. DESIGN: The growth rate and histologic characteristics of the SCC VII/SF cell line were initially determined in tissue culture experiments. Animal experiments were subsequently performed on C3H/HeJ mice. Using direct injection, 5 x 10(5) SCC VII/SF cells were delivered to the floor of the mouth of each animal. Animals were killed after 1, 2, and 3 weeks, and tumor growth, invasion, and regional and distant metastases were evaluated. RESULTS: Squamous cell carcinomas that could be palpated and measured externally were identified in the floor of the mouth of C3H/HeJ mice after 5 to 7 days. Local invasion into the mylohyoid musculature and mandible was present. Cervical lymph node and pulmonary metastases were identified between 2 and 3 weeks. CONCLUSIONS: This study introduces a new oral cancer animal model that shows initial locoregional tumor invasion, direct extension into the neck, early cervical metastases, and pulmonary metastases. These clinical and histopathologic attributes reflect the biological behavior and tumor progression seen in human oral cancer and therefore provide a model for clinically applicable research for primary and metastatic head and neck cancer.

L12 ANSWER 7 OF 13 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

95288854 EMBASE Document No.: 1995288854. Locoregional immunotherapy - Topics at the 13th and 14th meeting of the Japanese Research Society for Surgical Cancer Immunology. Amano S.; Kurosu Y.; Shibata M.. First Department of Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173, Japan. Biotherapy 9/7 (845-851) 1995. ISSN: 0914-2223. CODEN: BITPE. Pub. Country: Japan. Language: Japanese. Summary Language: English; Japanese.

AB Seventy papers concerning locoregional immunotherapy were presented at the 1992.apprx.1993 meetings. The subjects were head and neck cancer, breast cancer, lung cancer, gastric cancer, liver cancer, colon cancer, metastatic cancer, peritonitis carcinomatosa and experimental animal tumors. The methods of administration of BRMs were direct injection into the tumor or the regional lymph

**nodes**, or infusion into the hepatic artery or portal vein. Various BRMs were used (OK-432, PSK lentinan, IL-2, TNF, IFN- $\gamma$ , and mono-clonal antibody, such as missile therapy). New and hopeful challenges have been launched to overcome cancer growth, using the new techniques developed in the field of molecular biology, for example.

- L12 ANSWER 8 OF 13 SCISEARCH COPYRIGHT 2004 THOMSON ISI ON STN 93:661637 The Genuine Article (R) Number: MD940. A GENETIC APPROACH TO IDIOTYPIC VACCINATION. HAWKINS R E (Reprint); WINTER G; HAMBLIN T J; STEVENSON F K; RUSSELL S J. MRC, MOLEC BIOL LAB, HILLS RD, CAMBRIDGE CB2 2HQ, ENGLAND (Reprint); CTR PROT ENGN, CAMBRIDGE, ENGLAND; TENOVUS LAB, MOLEC IMMUNOL GRP, SOUTHAMPTON, ENGLAND. JOURNAL OF IMMUNOTHERAPY (NOV 1993) Vol. 14, No. 4, pp. 273-278. ISSN: 1053-8550. Pub. country: ENGLAND. Language: ENGLISH.
- \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\* Treatment of cancer with vaccines is an attractive prospect, but few AΒ tumours express suitable target antigens. With B-cell lymphomas, the idiotypic immunoglobulin (Ig) of the malignant B-cell should provide a suitable target but this requires a vaccine to be created for each patient. We propose a strategy for making such vaccines: first to clone the V genes of the idiotypic Ig, and second to inject the patient with the cloned DNA (genetic immunisation) in order to elicit an immune response against the encoded Ig. We have previously shown that the V genes of the idiotypic Ig can be identified from human lymph node biopsies by polymerase chain reaction amplification, cloning, and sequencing. In this report, we show that anti-idiotypic antibodies can be elicited by direct injection of an expression vector that encodes the V genes of murine antibodies (the V genes of B1.8, a murine hybridoma or of BCL1, a murine lymphoma line). This finding suggests a simple approach to the preparation of idiotypic vaccines for patients with B-cell lymphoma, which also circumvents the need for adjuvants.
- L12 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
  1993:465 Document No. 118:465 Study on immune response of lymphocytes in the regional lymph nodes of gastric cancer by direct injection of active charcoal-adsorbed β
  (1→3) glucan. Shibata, Kazunari; Suzuki, Kazunobu; Tsurui, Shigeru; Tanifuji, Kiminori (Dep. Surg., Tokyo Med. Coll., Tokyo, Japan). Tokyo Ika Daigaku Zasshi, 50(3), 443-53 (Japanese) 1992. CODEN: TIDZAH. ISSN: 0040-8905.
- Via an endoscope, active charcoal-adsorbed lentinan, lentinan, and active AΒ charcoal were locally applied to foci in 65 patients with curatively resectable gastric cancer before surgery, in an attempt to improve antitumoral activity of lymphocytes on the regional lymph nodes and to prevent malignant disease course progression. resulting immune response was then evaluated by determining the functions of lymph nodes by measuring the ratio of the composition of various T cell subgroups, IL-2 production, LAK cell activity, and NK cell Lentinan reinforced with adsorptive active charcoal particles had superior high lymph specificity and exerted a slow-release effect by accumulating in the regional lymph nodes via the lymph flow. In addition, this type of lentinan proved more effective than locally or systemically applied lentinan for increasing the immunol. competence of group I lymph nodes and raising lymphocyte antitumoral activity. Thus, supplementing lentinan with adsorptive active charcoal particles and locally applying it may be effective for preventing tumor metastasis.
- L12 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 1986:418611 Document No.: PREV198682094145; BA82:94145. THE ROLE OF THE PEYER'S PATCH IN CARCINOGENESIS I. THE ADSORPTION FROM THE GUT AND RETENTION OF 3 METHYLCHOLANTHRENE BY PEYER'S PATCHES. BOST K L [Reprint author]; CUCHENS M A. DEP OF MICROBIOL, UNIV OF MISSISSIPPI MED CENT, 2500 N STATE ST, JACKSON, MS 39216, USA. Carcinogenesis (Oxford), (1986) Vol. 7, No. 8, pp. 1251-1256.

CODEN: CRNGDP. ISSN: 0143-3334. Language: ENGLISH. Radiotracer methods were used to determine the distribution of AΒ 3-methylcholanthrene (3-MC) within the lymphoid organs of rats followingi.g. intubation, i.l. injection into the small intestine, i.v. injection or direct injection of the Peyer's patches with 3-[6-14C] methylcholanthrene (14C-MC). The data indicate that the gut-associated Peyer's patches and mesenteric lymph nodes were exposed to higher amounts of orally administered 14C-MC than any of the other lymphoid organs. Whereas the Peyer's patches exhibited the highest sp. act. for longer periods of time when low amounts of 14C-MC were administered, the sp. act. of the mesenteric lymph node were greater when rats were intubated with higher amounts of 14C-MC. Furthermore, the Peyer's patches were exposed to higher amounts of possible metabolites of 14C-MC. Injection of 14C-MC into the small intestinal lumen resulted in increased ratios of the Peyer's patch sp. act. to mesenteric lymph node sp. act., indicating that by-passing the stomach altered the distribution patterns. Data from rats injected i.v. with 14C-MC demonstrated that mesenteric lymph nodes but not Peyer's patches adsorbed and retained 14C-MC from the blood and indicated that the 14C-MC associated with Peyer's patches of i.g. treated rats was adsorbed from the gut rather than from the blood. Results obtained from rats which were exposed to 3-MC by directly injecting Peyer's patches with 14C-MC also indicated that the Peyer's patches were able to retain 3-MC once localized within this lymphoid organ, to metabolize the 3-MC and to possibly excrete the polycyclic aromatic hydrocarbon into the small intestine. Collectively the data indicate that Peyer's patches have an important role in the adsorption from the gut and subsequent retention of 3-MC and hence may be a likely target organ for lymphoid carcinogenesis following oral exposure to carcinogenic polycyclic aromatic hydrocarbons.

DUPLICATE 5 MEDLINE on STN L12 ANSWER 11 OF 13 Salvage of stage IV intraoral squamous cell PubMed ID: 3943008. 86105673. carcinomas with preoperative 5-fluorouracil. Ryan R F; Krementz E T; Truesdale G L. Cancer, (1986 Feb 15) 57 (4) 699-705. Journal code: 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English. A regimen for improving the salvage rate for Stage IV squamous cell carcinoma of the tongue, alveolar ridge and floor of mouth is presented. This method utilizes pre-operative sensitization of the tumor and regional lymph nodes by the topical application of 5-fluorouracil (5-FU) in the form of Efudex (Roche). The drug must be used topically at the tumor skin or tumor-mucous membrane interface to utilize the sensitizing properties of skin or mucous membrane. Further response is obtained by direct injections of 5-FU into the tumor. Later intravenous (IV) drip of 5-FU can be used particularly at the time of surgical resection. During the period of preparation until sensitized to 5-FU, patients must be restored to positive nitrogen balance and concurrent infections are controlled. Because of the importance of nutrition in restoring immunity, a feeding gastrostomy for these patients is recommended. The definitive surgery must include all bone that is involved, as 5-FU alone will not sterilize the bone. Of 15 patients who underwent the regimen outlined in this study, 12 of the patients with Stage IV intra-oral squamous cell carcinoma have had their primary tumor controlled for 17 months to 5 years at the time of this report.

L12 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1984:79567 Document No. 100:79567 Experimental study of local chemotherapy with topical injection of adriamycin. Muto, Fumitaka (1st Dep. Surg., Kyoto Prefect. Univ. Med., Kyoto, Japan). Kyoto-furitsu Ika Daigaku Zasshi, 92(12), 2027-36 (Japanese) 1983. CODEN: KFIZAO. ISSN: 0023-6012.

AB Local application of adriamycin [23214-92-8] is more efficient than i.v. injection in controlling lymph node metastasis and minimizing toxic side effects. This was demonstrated by injecting the

drug into rat gastric mucosa and showing a high concentration of the drug in the

stomach for a prolonged period with little toxic effect on the stomach. The concentration of adriamycin in the liver was considerably less than that observed after i.v. injection. In rats bearing AH-130 tumor in the foot pad, direct injection of adriamycin into the tumor increased the survival rate and had a greater efficacy than did the i.v. injection.

L12 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN

1949:15666 Document No. 43:15666 Original Reference No. 43:3095b-e The development of tumors in various tissues in mice following direct application of a carcinogenic hydrocarbon. Rask-Nielsen, Ragna Acta Path. Microbiol. Scand., Suppl., 78, 1-144 (Unavailable) 1948.

B Direct injection of a small amount of 9,10-dimethyl-1,2-benzanthracene into various organs of mice indicates that the thymus gland and lung are more susceptible than any of the other tissues which produce tumors spontaneously (subcutaneous tissue, skin, mammary tissue). Direct injection of large doses of this carcinogen into various organs induced tumors in thymus gland, lung, and also subcutaneous tissue but not in the other tissues capable of spontaneous tumor formation, or in those not capable of spontaneous tumor formation (lymph nodes, spleen, bone marrow, kidney and testis) with the exception of one testicular sarcoma. Nonlocal tumor formation was observed in thymus gland and lung, with leukemic infiltration only, in lymph nodes and spleen. Carcinogenic agents do not produce tumors in tissues incapable of the spontaneous generation of tumors.

=> s CTL response L13 14984 CTL RESPONSE

=> s l13 and direct injection L14 27 L13 AND DIRECT INJECTION

=> s l14 and lymph node L15 0 L14 AND LYMPH NODE

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L17 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
2004:313774 Enhancement of HBV gene-induced specific cell-mediated
immunoresponse by C3d-P28. Wang, Lixin; Xu, Wei; Guan, Qingdong; Xiong,
Sidong (Shanghai Medical College, Fudan University, Shanghai, 200032,
Peop. Rep. China). Xibao Yu Fenzi Mianyixue Zazhi, 19(3), 242-244
(Chinese) 2003. CODEN: XFMZFM. ISSN: 1007-8738. Publisher: Xibao Yu
Fenzi Mianyixue Zazhi Bianjibu.

To investigate whether P28 derived from complement C3d can enhance the cell-mediated immunoresponse to HBV-preS2/S induced by direct injection of naked plasmid DNA containing four tandem repeats of C3d-P28 gene and HBV-preS2/S gene existed in fusion form. Four copies of gene coding for C3d-P28, amplified by PCR and cut by restriction endonucleases digestion, were subcloned into a eukaryotic expression vector pVAON33 to construct pVAON33-P28.4. HBV-preS2/S gene was then introduced into the pVAON33 and pVAON33-P28.4 resp. to form pVAON33-S2/S and pVAON33-S2/S-P28.4. The recombinant plasmids were identified by PCR

and restriction endonucleases digestion as well as DNA sequencing. BALB/c mice were immunized I.m. three times at 3 wk' intervals with 100 µg of pVAON33-S2/S DNA, pVAON33-S2/S-P28.4 and mock DNA, resp. Splenocytes from immunized mice were stimulated by HBsAg and then harvested to analyze the specific lymphocytic proliferative response and CTL cytotoxic activity by 3H-TdR incorporation assay and isotopic release anal., resp. Specific lymphocytic proliferation and CTL cytotoxic activity against HBV-preS2/S were observed in mice immunized by both pVAON33-S2/S and pVAON33-S2/S-P28.4 in dose-dependent form. Specific lymphocytic proliferation and CTL response in mice immunized by pVAON33-S2/S-P28.4 were markedly stronger than those in mice immunized by pVAON33-S2/S. A C3d-P28 can enhance the cell-mediated immunoresponse induced by HBV-preS2/S gene immunization.

- L17 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1
  2000031176. PubMed ID: 10566900. RNA melanoma vaccine: induction of
  antitumor immunity by human glycoprotein 100 mRNA immunization. Zhou W Z;
  Hoon D S; Huang S K; Fujii S; Hashimoto K; Morishita R; Kaneda Y.
  (Division of Gene Therapy Science, Osaka University School of Medicine,
  Suita, Japan.) Human gene therapy, (1999 Nov 1) 10 (16) 2719-24. Journal
  code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language:
  English.
- An RNA melanoma vaccine was investigated to induce protective immunity in a mouse-melanoma model. LacZ mRNA was synthesized in vitro by pSFV3 expression vector and introduced into the spleen of mice, using HVJ-liposomes. A high level of beta-galactosidase activity was detected for 10 days in mouse spleen. The human melanoma-associated antigen gp100 mRNA was synthesized in vitro by pSFV3 vector and encapsulated in HVJ-liposomes. Immunization by direct injection of the gp100 mRNA HVJ-liposomes into mouse spleen induced both anti-gp100 Ab and CTL responses against B16 melanoma. Immunization by administration of gp100 mRNA into the spleen delayed tumor growth and significantly prolonged survival compared with control treated mice. These preclinical studies demonstrate that an RNA tumor antigen vaccine strategy has potential application for human cancer treatment and prevention.
- L17 ANSWER 3 OF 7 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
  1999:224191 The Genuine Article (R) Number: 175YD. Enhanced cellular immunity
  to hepatitis C virus nonstructural proteins by codelivery of granulocyte
  macrophage-colony stimulating factor gene in intramuscular DNA
  immunization. Cho J H; Lee S W; Sung Y C (Reprint). POHANG UNIV SCI &
  TECHNOL, SCH ENVIRONM ENGN, CTR BIOFUNCT MOL, DEPT LIFE SCI, SAN 31,
  POHANG 790784, KYUNGBUK, SOUTH KOREA (Reprint); POHANG UNIV SCI & TECHNOL,
  SCH ENVIRONM ENGN, CTR BIOFUNCT MOL, DEPT LIFE SCI, POHANG 790784,
  KYUNGBUK, SOUTH KOREA. VACCINE (5 MAR 1999) Vol. 17, No. 9-10, pp.
  1136-1144. Publisher: ELSEVIER SCI LTD. THE BOULEVARD, LANGFORD LANE,
  KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0264-410X. Pub. country:
  SOUTH KOREA. Language: English.
  \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*
- Hepatitis C virus (HCV) nonstructural (NS) proteins appeared to be ΑB important targets for HCV vaccine development, since NS-specific T-helper-cell responses are associated with clearance from acute HCV infection. In this report, we have constructed a plasmid, pTV-NS345, that encodes the HCV NS3, NS4 and NS5 proteins (NS345) and a bicistronic plasmid, PIV-NS345/GMCSF, in which the HCV NS345 polyprotein and GMCSF are translated independently. Intramuscular inoculation with pTV-NS345 plasmid DNA into the Buffalo rats generated both antibody and T-cell proliferative responses to each NS protein. The expression of GMCSF, together with HCV NS345 proteins, appeared to significantly increase T-cell proliferative responses. In particular, the inoculation of a bicistronic plasmid generated higher T-cell proliferative responses to each NS protein than did the coinjection of two separate plasmids, pTV-NS345 and pTV-GMCSF. These results demonstrate that the codelivery of GMCSF augmented HCV NS345-specific cellular immunity and that the intensity of the immunity

was differed depending on how GMCSF gene is codelivered. (C) 1999 Elsevier Science Ltd. All rights reserved.

DUPLICATE 2 L17 ANSWER 4 OF 7 MEDLINE on STN Similarity of strain- and route-dependent 1998286926. PubMed ID: 9625262. murine responses to an adenovirus vector using the homologous thrombopoietin cDNA as the reporter genes. Suzuki M; Singh R; Moore M A; Song W R; Crystal R G. (Division of Pulmonary and Critical Care Medicine, The New York Hospital-Cornell Medical Center, NY 10021, USA. ) Human gene therapy, (1998 May 20) 9 (8) 1223-31. Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English. Replication-deficient adenovirus (Ad) vectors are effective in AB transferring genes in vivo, but their use is associated with significant variation in the extent and/or duration of expression observed among different strains of experimental animals and different routes of administration of the vector. We have minimized the variables of the heterologous transgene and animal-to-animal variation by constructing an Ad vector encoding murine thrombopoietin (mTPO, AdmTPO), a homologous protein that induces a physiologic response (elevation of blood platelet levels) that can be followed sequentially over time in the same animal. Using the C57BL/6 and BALB/c stains, liver administration was accomplished by intravenous administration and skeletal muscle administration by direct injection. Despite the use of a homologous cDNA as a transgene, the Ad genome was rapidly lost from the liver after intravenous administration over the first 1 to 2 weeks, with no difference in pattern of decline between the C57BL/6 and BALB/c strains. Both strains exhibited a cytotoxic T lymphocyte (CTL) response directed against the AdmTPO vector. Consistent with the decline in vector genome over time, the initial high levels of mTPO mRNA in the liver declined to an undetectable level within 2 weeks. Platelet counts peaked at 8- to 10-fold above baseline within the first 2 weeks, and then gradually declined, returning to normal level by 50 to 60 days. Intravenous administration of the AdmTPO vector to beta2-microglobulindeficient mice resulted in a longer persistence of elevated platelets levels, although the eventual return of platelet levels to normal in these mice suggests the elimination of the Ad vector cannot be explained solely by CTL response. Although the intramuscular administration of the AdmTPO vector resulted in platelet levels with a lower peak and minor differences over time compared with the intravenous route, the C57BL/6 and BALB/c strains demonstrated the same rapid loss of Ad genome and mTPO mRNA levels in the muscle as in the liver. Together, these observations suggest that simplifying the experimental design by eliminating the variable of host response to a heterologous transgene, and by following the consequences of gene transfer in the same animals over time, there can be remarkable similarity in strain- and route-dependent responses to an Ad vector.

L17 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 3
96234392. PubMed ID: 8640771. Protection against a lethal challenge with
SV40-transformed cells by the **direct injection** of
DNA-encoding SV40 large tumor antigen. Bright R K; Beames B; Shearer M H;
Kennedy R C. (Department of Virology and Immunology, Southwest Foundation
for Biomedical Research, San Antonio, Texas 78228, USA.) Cancer research,
(1996 Mar 1) 56 (5) 1126-30. Journal code: 2984705R. ISSN: 0008-5472.
Pub. country: United States. Language: English.

AB Plasmid DNA encoding the large tumor antigen (T- ag) of SV40 was used to actively immunize mice to assess the induction of SV40 T-ag-specific immunity. Mice were injected with the naked DNA i.m., and immune responses were compared to those elicited in mice immunized with the recombinant SV40 T-ag protein. Compared to immunization with the recombinant protein, naked DNA induced weak antibody responses to SV40 T-ag. No increase in natural killer cell activity was observed following either recombinant protein or nucleic acid vaccination. However, the recombinant SV40 T-ag failed to induce SV40 T-ag-specific CTL responses, whereas the plasmid DNA encoding SV40 T-ag elicited CTL

activity specific for SV40 T-ag. The SV40 T-ag-specific CTL lysed in vitro only syngeneic target cells (H-2(d)) expressing SV40 T-ag, indicating that the CTL are MHC restricted. Both the recombinant protein and naked DNA preparations induced immune responses that were protective against a lethal challenge with syngeneic SV40-transformed cells. A comparison of recombinant protein versus nucleic acid immunization indicates that both humoral and cell-mediated immune responses may play a role in SV40 T-ag immunity. These data indicate that active immunization with genes encoding tumor-specific antigens may be an efficacious strategy for the induction of tumor immunity.

MEDLINE on STN DUPLICATE 4 L17 ANSWER 6 OF 7 PubMed ID: 7492440. Induction of potent humoral and 96020094. cell-mediated immune responses following direct injection of DNA encoding the HIV type 1 env and rev gene products. Okuda K; Bukawa H; Hamajima K; Kawamoto S; Sekigawa K; Yamada Y; Tanaka S; Ishi N; Aoki I; Nakamura M. (Department of Bacteriology, Yokohama City University School of Medicine, Japan. ) AIDS research and human retroviruses, (1995 Aug) 11 (8) 933-43. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English. DNA vaccines have the potential of giving rise to a potent cell-mediated immune response by inducing intracellular synthesis and subsequent antigenic presentation of encoded antigens. We have tested a DNA vaccine specific for human immunodeficiency virus type 1 (HIV-1) by the injection of animals with expression plasmids encoding the HIV-1 envelope protein and the Rev regulatory protein. Injection of both plasmids into mice, rabbits, or macaques was found to induce high levels of specific antibodies capable of efficiently inhibiting both HIV-1 infection and envelope-mediated cell fusion. A readily detectable delayed-type hypersensitivity (DTH) response was demonstrable in injected mice and lymphocytes derived from these proliferated in response to an HIV-1 envelope V3 loop-specific peptide. Interestingly, the injected mice or macaques also developed a strong cytotoxic T lymphocyte (CTL) response against target cells pulsed with the V3 peptide. Taken together, these data demonstrate that injection of HIV-1 gene expression plasmids can induce potent humoral and cell-mediated immune responses and suggest that DNA vaccines may prove to be significantly beneficial as a means of immunizing against HIV-1.

L17 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 5
94309169. PubMed ID: 8035504. Direct injection of a
recombinant retroviral vector induces human immunodeficiency
virus-specific immune responses in mice and nonhuman primates. Irwin M J;
Laube L S; Lee V; Austin M; Chada S; Anderson C G; Townsend K; Jolly D J;
Warner J F. (Department of Immunobiology, Viagene, Inc., San Diego,
California 92121.) Journal of virology, (1994 Aug) 68 (8) 5036-44.
Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States.
Language: English.

The cytotoxic T-lymphocyte (CTL) response plays an AB important role in controlling the severity and duration of viral infections. Immunization by direct in vivo administration of retroviral vector particles represents an efficient means of introducing and expressing genes and, subsequently, the proteins they encode in vivo in mammalian cells. In this manner foreign proteins can be provided to the endogenous, class I major histocompatibility complex antigen presentation pathway leading to CTL activation. A nonreplicating recombinant retroviral vector, encoding the human immunodeficiency virus type 1 (HIV-1) IIIB envelope and rev proteins, has been developed and examined for stimulation of immune responses in mouse, rhesus macaque, and baboon models. Animals were immunized by direct intramuscular injection of the retroviral vector particles. Vector-immunized mice, macaques, and baboons generated long-lived CD8+, major histocompatibility complex-restricted CTL responses that were HIV-1 protein specific. The CTL responses were found to be dependent on the ability of the retroviral vector to transduce cells. The vector also elicited

HIV-1 envelope-specific antibody responses in mice and baboons. These studies demonstrate the ability of a retroviral vector encoding HIV-1 proteins to stimulate cellular and humoral immune responses and suggest that retrovector immunization may provide an effective means of inducing or augmenting CTL responses in HIV-1-infected individuals.

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(FILE 'HOME' ENTERED AT 14:05:12 ON 12 MAY 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:05:25 ON 12 MAY 2004

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0 S FOLICLE INJECTION
L1
L2
         354385 S LYMPH NODE
          20700 S L2 AND INJECTION
L3
            192 S L3 AND CTL RESPONSE
L4
             11 S L4 AND DIRECTLY
L5
              3 DUP REMOVE L5 (8 DUPLICATES REMOVED)
L6
            101 S L2 AND DIRECT INJECTION
L7
             10 S L7 AND LYMPH VESSEL
L8
              9 DUP REMOVE L8 (1 DUPLICATE REMOVED)
L9
              0 S L7 AND CTL RESPONSE
L10
             27 S L7 AND TUMOR
L11
             13 DUP REMOVE L11 (14 DUPLICATES REMOVED)
L12
          14984 S CTL RESPONSE
L13
            27 S L13 AND DIRECT INJECTION
L14
              0 S L14 AND LYMPH NODE
L15
              0 S L14 AND LYMPH VESSEL
L16
              7 DUP REMOVE L14 (20 DUPLICATES REMOVED)
L17
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PROCESSING COMPLETED FOR L4
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=> s l18 and antitumor
             4 L18 AND ANTITUMOR
L19
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=> dup remove 119
PROCESSING COMPLETED FOR L19
L20 4 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d 120 1-4 cbib abs

L20 ANSWER 1 OF 4 MEDLINE on STN
2004034900. PubMed ID: 14734732. IL-21 induces tumor rejection by specific CTL and IFN-gamma-dependent CXC chemokines in syngeneic mice. Di Carlo Emma; Comes Alberto; Orengo Anna Maria; Rosso Ombretta; Meazza Raffaella; Musiani Piero; Colombo Mario P; Ferrini Silvano. (Dipartimento di Oncologia e Neuroscienze, Universita di Chieti, Chieti, Italy.) Journal of immunology (Baltimore, Md.: 1950), (2004 Feb 1) 172 (3) 1540-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB IL-21 is an immune-stimulatory four alpha helix cytokine produced by activated T cells. To study the in vivo antitumor activities of IL-21, TS/A murine mammary adenocarcinoma cells were genetically modified to secrete IL-21 (TS/A-IL-21). These cells developed small tumors that were subsequently rejected by 90% of s.c. injected syngeneic mice. Five days after injection, TS/A-IL-21 tumors showed numerous infiltrating granulocytes, NK cells, and to a lesser extent CD8(+) T cells, along with the expression of TNF-alpha, IFN-gamma, and endothelial adhesion molecules ICAM-1 and VCAM-1. At day 7, CD8(+) and CD4(+) T cells increased together with IFN-gamma, and the CXC chemokines IFN-gamma-inducible protein 10, monokine induced by IFN-gamma, and

IFN-inducible T cell alpha-chemoattractant. The TS/A-IL-21 tumor displayed a disrupted vascular network with abortive sprouting and signs of endothelial cell damage. In vivo depletion experiments by specific Abs showed that rejection of TS/A-IL-21 cells required CD8(+) T lymphocytes and granulocytes. When injected in IFN-gamma-deficient mice, TS/A-IL-21 cells formed tumors that regressed in only 29% of animals, indicating a role for IFN-gamma in IL-21-mediated antitumor response, but also the existence of IFN-gamma-independent effects. Most immunocompetent mice rejecting TS/A-IL-21 cells developed protective immunity against TS/A-pc (75%) and against the antigenically related C26 colon carcinoma cells (61%), as indicated by rechallenge experiments. A specific CTL response against the gp70-env protein of an endogenous murine retrovirus coexpressed by TS/A and C26 cells was detected in mice rejecting TS/A-IL-21 cells. These data suggest that IL-21 represents a suitable adjuvant in inducing specific CTL responses.

L20 ANSWER 2 OF 4 MEDLINE on STN IL-2 intratumoral immunotherapy enhances PubMed ID: 14607902. 2003544503. CD8+ T cells that mediate destruction of tumor cells and tumor-associated vasculature: a novel mechanism for IL-2. Jackaman Connie; Bundell Christine S; Kinnear Beverley F; Smith Alison M; Filion Pierre; van Hagen Deborah; Robinson Bruce W S; Nelson Delia J. (School of Medicine and Pharmacology, University of Western Australia. ) Journal of immunology (Baltimore, Md.: 1950), (2003 Nov 15) 171 (10) 5051-63. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English. Therapeutic use of IL-2 can generate antitumor immunity; AB however, a variety of different mechanisms have been reported. We injected IL-2 intratumorally (i.t.) at different stages of growth, using our unique murine model of mesothelioma (AE17; and AE17 transfected with secretory OVA (AE17-sOVA)), and systematically analyzed real-time events as they occurred in vivo. The majority of mice with small tumors when treatment commenced displayed complete tumor regression, remained tumor free for >2 mo, and survived rechallenge with AE17 tumor cells. However, mice with large tumors at the start of treatment failed to respond. Timing experiments showed that IL-2-mediated responses were dependent upon tumor size, not on the duration of disease. Although i.t. IL-2 did not alter tumor Ag presentation in draining lymph nodes, it did enhance a previously primed, endogenous, tumor-specific in vivo CTL response that coincided with regressing tumors. Both CD4(+) and CD8(+) cells were required for IL-2-mediated tumor eradication, because IL-2 therapy failed in CD4(+)-depleted, CD8(+)-depleted, and both CD4(+)- and CD8(+)-depleted C57BL/6J animals. Tumor-infiltrating CD8(+) T cells, but not CD4(+) T cells, increased in association with a marked reduction in tumor-associated vascularity. Destruction of blood vessels required CD8(+) T cells, because this did not occur in nude mice or in CD8(+)-depleted C57BL/6J mice. These results show that repeated doses of i.t. (but not systemic) IL-2 mediates tumor regression via an enhanced endogenous tumor-specific CTL response concomitant with reduced vasculature, thereby demonstrating a novel mechanism for IL-2 activity.

MEDLINE on STN L20 ANSWER 3 OF 4 PubMed ID: 10706699. CD8+ T cell-dependent elimination of 2000171509. dendritic cells in vivo limits the induction of antitumor immunity. Hermans I F; Ritchie D S; Yang J; Roberts J M; Ronchese F. (Malaghan Institute of Medical Research, Wellington School of Medicine, Wellington, New Zealand. ) Journal of immunology (Baltimore, Md. : 1950), (2000 Mar 15) 164 (6) 3095-101. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English. The fate of dendritic cells (DC) after they have initiated a T cell immune AΒ response is still undefined. We have monitored the migration of DC labeled with a fluorescent tracer and injected s.c. into naive mice or into mice with an ongoing immune response. DC not loaded with Ag were detected in the draining lymph node in excess of 7

days after injection with maximum numbers detectable approximately 40 h after transfer. In contrast, DC that had been loaded with an MHC class I-binding peptide disappeared from the lymph node with kinetics that parallel the known kinetics of activation of CD8+ T cells to effector function. In the presence of high numbers of specific CTL precursors, as in TCR transgenic mice, DC numbers were significantly decreased by 72 h after injection. The rate of DC disappearance was extremely rapid and efficient in recently immunized mice and was slower in "memory" mice in which memory CD8+ cells needed to reacquire effector function before mediating DC elimination. We also show that CTL-mediated clearance of Ag-loaded DC has a notable effect on immune responses in vivo. Ag-specific CD8+ T cells failed to divide in response to Ag presented on a DC if the DC were targets of a pre-existing CTL response. The induction of antitumor immunity by tumor Ag-loaded DC was also impaired. Therefore, CTL-mediated clearance of Ag-loaded DC may serve as a negative feedback mechanism to limit the activity of DC within the lymph node.

L20 ANSWER 4 OF 4 MEDLINE on STN
2000005758. PubMed ID: 10537366. Antibodies to vascular endothelial growth factor enhance the efficacy of cancer immunotherapy by improving endogenous dendritic cell function. Gabrilovich D I; Ishida T; Nadaf S; Ohm J E; Carbone D P. (Department of Medicine and The Vanderbilt Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-6838, USA.. dgabril@luc.edu). Clinical cancer research: an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10) 2963-70. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

Inadequate function of dendritic cells (DCs) in tumor-bearing hosts is one mechanism of tumor escape from immune system control and may compromise the efficacy of cancer immunotherapy. Vascular endothelial growth factor (VEGF), produced by most tumors, not only plays an important role in tumor angiogenesis but also can inhibit the maturation of DCs from hematopoietic progenitors. Here, we investigate a novel combination of antiangiogenic and immunotherapy based on this dual role of VEGF. Two s.c. mouse tumor models were used: D459 cells, expressing mutant human p53; and MethA sarcoma with point mutations in the endogenous murine p53 gene. Therapy with anti-mouse VEGF antibody (10 microg i.p. twice a week over 4 weeks) was initiated when tumors became palpable. Treatment of established tumors with anti-VEGF antibody alone did not affect the rate of tumor growth. However, anti-VEGF antibody significantly improved the number and function of lymph node and spleen DCs in these tumor-bearing animals. To investigate the possible effects of this antibody on the immunotherapy of established tumors, tumor-bearing mice were immunized with DCs pulsed with the corresponding mutation-specific p53 peptides, together with injections of anti-VEGF antibody. Therapy with peptide-pulsed DCs alone resulted in considerable slowing of tumor growth but only during the period of treatment, and tumor growth resumed after the end of the therapy. Combined treatment with peptide-pulsed DCs and anti-VEGF antibody resulted in a prolonged and much more pronounced antitumor effect. This effect was associated with the induction of significant anti-p53 CTL responses only in this group of mice. These data suggest that inhibition of VEGF may be a valuable adjuvant in the immunotherapy of cancer.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:05:25 ON 12 MAY 2004

L1 0 S FOLICLE INJECTION

L2 354385 S LYMPH NODE

L3 20700 S L2 AND INJECTION

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192 S L3 AND CTL RESPONSE
L4
L5
             11 S L4 AND DIRECTLY
              3 DUP REMOVE L5 (8 DUPLICATES REMOVED)
L6
            101 S L2 AND DIRECT INJECTION
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L8
             10 S L7 AND LYMPH VESSEL
L9
              9 DUP REMOVE L8 (1 DUPLICATE REMOVED)
              0 S L7 AND CTL RESPONSE
L10
             27 S L7 AND TUMOR
T<sub>1</sub>11
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          14984 S CTL RESPONSE
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             27 S L13 AND DIRECT INJECTION
L14
              0 S L14 AND LYMPH NODE
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              0 S L14 AND LYMPH VESSEL
L16
              7 DUP REMOVE L14 (20 DUPLICATES REMOVED)
L17
             64 DUP REMOVE L4 (128 DUPLICATES REMOVED)
L18
              4 S L18 AND ANTITUMOR
L19
              4 DUP REMOVE L19 (0 DUPLICATES REMOVED)
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           101 L2 AND DIRECT INJECTION
L21
=> dup remove 121
PROCESSING COMPLETED FOR L21
             50 DUP REMOVE L21 (51 DUPLICATES REMOVED)
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=> d 122 1-50 cbib abs

L22 ANSWER 1 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

ON STN DUPLICATE 1

2004113784 EMBASE Optimised nuclear medicine method for tumour marking and sentinel node detection in occult primary breast lesions. De Cicco C.; Trifiro G.; Intra M.; Marotta G.; Ciprian A.; Frasson A.; Prisco G.; Luini A.; Viale G.; Paganelli G.. C. De Cicco, Division of Nuclear Medicine, European Institute of Oncology, University of Milan, Via Ripamonti, 435-20141 Milan, Italy. concetta.de-cicco@ieo.it. European Journal of Nuclear Medicine and Molecular Imaging 31/3 (349-354) 2004. Refs: 17.

ISSN: 1619-7070. CODEN: EJNMA6. Pub. Country: Germany. Language: English. Summary Language: English.

AB The aim of this study was to evaluate the feasibility of sentinel node (SN) biopsy in occult breast lesions with different radiopharmaceuticals and to establish the optimal lymphoscintigraphic method to detect both occult lesions and SNs (SNOLL: sentinel node and occult lesion localisation). Two hundred and twenty-seven consecutive patients suspected to have clinically occult breast carcinoma were enrolled in the study. In addition to the radioquided occult lesion localisation (ROLL) procedure, using macroaggregates of technetium-99m labelled human serum albumin (MAA) injected directly into the lesion, lymphoscintigraphy was performed with nanocolloids (NC) injected in a peritumoral (group I) or a subdermal site (group II). In group III, a sole injection of NC was done into the lesion in order to perform both ROLL and SNOLL. Overall, axillary SNs were identified in 205 of the 227 patients (90.3%). In 12/62 (19.4%) patients of group I and 9/79 (11.4%) patients of group III, radioactive nodes were not visualised, whereas SNs were successfully localised in 85 of 86 patients of group II (P<0.001). Pathological findings revealed breast carcinoma in 148/227 patients (65.2%) and benign lesions in 79 (34.8%). A total of 131 axillary SNs were removed in 118 patients with breast carcinoma; intraoperative examination of the SNs revealed metastatic involvement in 16 out of 96 cases of invasive c arcinoma (16.7%). It is concluded that the combination of the ROLL procedure with direct injection of MAA into the lesion and lymphoscintigraphy performed with subdermal injection of radiocolloids represents the method of choice for accurate localisation of both non-palpable lesions and SNs.

- 2002:276188 Document No. 136:289366 Use of VEGF as a lymphangiogenic agents
   to treat lymphatic disorders. Gravereaux, Edwin C.; Silver, Marcy; Isner,
   Jeffrey M.; Yoon, Young-Sup (St. Elizabeth's Medical Center of Boston,
   Inc., USA). PCT Int. Appl. WO 2002029087 A2 20020411, 77 pp. DESIGNATED
   STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
   CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
   HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
   MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
   SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,
   KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK,
   ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD,
   TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US30904
   20011002. PRIORITY: US 2000-PV237171 20001002.
- The present invention provides methods for promoting the growth of new lymph vessels (lymphangiogenesis). Generally, such methods include administering at least one vascular endothelian factor (VEGF) such as VEGF-2. In one embodiment, therapeutic methods for treating lymphedema and related disorders in a human patient are disclosed. The VEGF can be provided by any suitable means including direct injection of a nucleic acid encoding same or an active fragment thereof. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new lymph vessel growth. Addnl., the rabbit VEGFR-3 cDNA and protein are both claimed.
- L22 ANSWER 3 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN
  2002:794299 Document No. 137:320695 Use of VEGFs as lymphangiogenic agents to treat lymphatic disorders. Gravereaux, Edwin C.; Silver, Marcy; Yoon, Young-sup; Isner, Jeffrey M.; Isner, Linda (St. Elizabeth's Medical Center of Boston, Inc., USA). U.S. Pat. Appl. Publ. US 2002151489 A1 20021017, 54 pp., Cont.-in-part of U. S. Provisional Ser. No. 237,171. (English). CODEN: USXXCO. APPLICATION: US 2001-970088 20011002. PRIORITY: US 2000-PV237171 20001002.
- The present invention provides methods for promoting the growth of new lymph vessels (lymphangiogenesis). Generally, such methods include administering at least one vascular endothelian factor (VEGF) such as VEGF-2. In one embodiment, therapeutic methods for treating lymphedema and related disorders in a human patient are disclosed. The VEGF can be provided by any suitable means including direct injection of a nucleic acid encoding same or an active fragment thereof. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new lymph vessel growth. Also provided are pharmaceutical products for promoting lymphangiogenesis as well as a test system for screening compds. capable of inducing new lymph vessel growth. Addnl., fragments of the rabbit VEGFR-3 cDNA and protein are both claimed.
- L22 ANSWER 4 OF 50 MEDLINE on STN DUPLICATE 2
  2002451907. PubMed ID: 12209648. Lack of antigen-specific immune responses in anti-IL-7 receptor alpha chain antibody-treated Peyer's patch-null mice following intestinal immunization with microencapsulated antigen. Kunisawa Jun; Takahashi Ichiro; Okudaira Akiko; Hiroi Takachika; Katayama Kazufumi; Ariyama Teruko; Tsutsumi Yasuo; Nakagawa Shinsaku; Kiyono Hiroshi; Mayumi Tadanori. (Department of Mucosal Immunology, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan.) European journal of immunology, (2002 Aug) 32 (8) 2347-55. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.
- Peyer's patches (PP) represent a well-characterized inductive site in gut-associated lymphoid tissue that actively acquires antigens from the intestinal lumen. It was reported that organized PP are not required for antigen-specific IgA responses induced by oral immunization with soluble antigen mixed with the mucosal adjuvant, cholera toxin. However, the role of PP in the induction of mucosal and systemic immune responses remains to be clarified in the case of particulate antigen. Here, we created PP-null

mice by treating them with monoclonal anti-IL-7 receptor alpha chain (IL-7 R alpha) antibody during gestation and then immunized with antigen-encapsulated poly-lactic acid (PLA) microspheres. Brisk OVA-specific antibody responses were noted in serum and fecal extracts of normal mice following direct intestinal immunization with OVA in PBS (OVA-PBS) as well as in PLA-microspheres (OVA-MS). Antibody production was similarly elevated in PP-null mice immunized with OVA-PBS via direct injection into the intestinal tract. In contrast, OVA-specific antibody responses were dramatically decreased in both serum and fecal extracts collected from PP-null mice immunized intestinally with OVA-MS. These results were further supported by the number of OVA-specific antibody-forming cells detected in the spleen and intestinal lamina propria. PP deficiency also resulted in the reduction in OVA-specific Th1/Th2 cell responses in the spleen and mesenteric lymph nodes of mice intestinally immunized with OVA-MS. These results suggested that organized PP do, in fact, play a crucial role in the induction of antigen-specific immune responses against ingested particulate antigen.

L22 ANSWER 5 OF 50 MEDLINE on STN DUPLICATE 3
2002383730. PubMed ID: 12133274. Oncolytic herpesvirus effectively treats
murine squamous cell carcinoma and spreads by natural lymphatics to treat
sites of lymphatic metastases. Wong Richard J; Joe John K; Kim Se-Heon;
Shah Jatin P; Horsburgh Brian; Fong Yuman. (Head and Neck Service,
Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York,
NY 10021, USA.) Human gene therapy, (2002 Jul 1) 13 (10) 1213-23.
Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States.

Language: English. Oncolytic herpesviruses have significant antitumoral effects in animal models when delivered directly to established tumors. Lymphatic metastases are a common occurrence for many tumor types. This study investigates the potential of an attenuated, replication-competent, oncolytic herpes simplex virus (NV1023) both to treat a primary tumor by direct injection and to travel through the lymphatic system to treat metastatic tumor within the lymph nodes draining lymph from the site of primary cancer. Isosulfan blue dye was injected into murine auricles to determine normal lymphatic drainage patterns and demonstrated consistent blue staining of a group of ipsilateral cervical lymph nodes. Auricular injections of NV1023 resulted in viral transit to these lymph nodes as measured by 5-bromo-4-chloro-3-indolyl-beta-Dgalactopyranoside histochemistry and viral plaque assay. An oncolytic herpesvirus (NV1066) expressing green fluorescent protein also demonstrated viral transit from the auricle to the cervical lymph nodes on fluorescence microscopy. Using the SCC VII cell line, a novel murine model of auricular squamous cell carcinoma was developed with an approximately 20% incidence of cervical lymph node metastases. Delivery of NV1023 or NV1066 to the surgical beds after excision of auricular SCC VII tumors resulted in successful viral infection of metastatic SCC VII cells within the cervical lymph nodes. After a 7-week follow-up, significantly enhanced locoregional control (p < 0.05, Fisher exact test) and disease-free survival (p < 0.05, log rank test) were evident with NV1023 treatment. This study demonstrates that the delivery of an oncolytic herpesvirus to a primary tumor site after surgical excision may have a significant impact on reducing both primary site recurrence and regional nodal metastases.

L22 ANSWER 6 OF 50 MEDLINE on STN DUPLICATE 4
2002182449. PubMed ID: 11916241. Suppression of murine mammary carcinoma
growth and metastasis by HSVtk/GCV gene therapy using in vivo
electroporation. Shibata Masa-Aki; Morimoto Junji; Otsuki Yoshinori.
(Department of Anatomy and Biology, Osaka Medical College, Takatsuki,
Japan.) Cancer gene therapy, (2002 Jan) 9 (1) 16-27. Journal code:
9432230. ISSN: 0929-1903. Pub. country: England: United Kingdom. Language:
English.

The effectiveness of electroporation as a means of gene transfection, both AB in vitro and in vivo, was tested using the herpes simplex virus 1 thymidine kinase (HSVtk) gene in combination with ganciclovir (GCV) administration as therapy against murine mammary cancer. Approximately 80% of BJMC3879 metastatic mammary carcinoma cells, derived from MMTV-infected BALB/c mice, died as a result of HSVtk/GCV treatment 72 hours after the transfection; decreased DNA synthesis was also seen. Mammary tumors induced by inoculation of syngeneic mice with BJMC3879 cells were subsequently treated by direct injection of vector containing HSVtk (pHSVtk) alone, empty vector or saline alone twice a week. After each injection, the tumors were subjected to in vivo electroporation. Mice treated with pHSVtk or saline were intraperitoneally injected with GCV at 40 mg/kg five times a week. Significantly reduced tumor volumes were observed for the pHSVtk+GCV group in experimental week 2 and thereafter throughout the 2-month study. DNA synthesis was significantly decreased as well in the pHSVtk+GCV group compared with all other groups. Furthermore, metastasis to lymph nodes and lungs was significantly suppressed by HSVtk/GCV treatment. Expression of HSVtk in the tumors was confirmed by RT-PCR. Macrophage accumulations were frequently observed in the peripheries of necrotic regions in HSVtk/GCV-treated tumors, where levels of apoptosis were significantly higher than those observed in other groups. We therefore conclude that in vivo electroporation can result in efficient gene transfer and that the HSVtk/GCV prodrug system strongly suppresses tumor growth and metastases in this model.

L22 ANSWER 7 OF 50 MEDLINE on STN

2001653877. PubMed ID: 11706493. [Lymphadenography--pioneering work of
Sven Bruun and Arnfinn Engeset]. Lymfadenografi--pionerarbeid av Sven
Bruun og Arnfinn Engeset. Kolbenstvedt A. (Radiologisk avdeling
Rikshospitalet 0027 Oslo.) Tidsskrift for den Norske laegeforening, (2001
Oct 10) 121 (24) 2836-7. Journal code: 0413423. ISSN: 0029-2001. Pub.
country: Norway. Language: Norwegian.

Lymphadenography is a method for direct radiologic visualization of AΒ lymph nodes following injection of fat soluble contrast medium. Sven Bruun and Arnfinn Engeset at Rogaland Hospital developed this method in 1952 and published preliminary results in 1956. They have been somewhat overshadowed by the English surgeon John B. Kinmonth who published his method on lymphangiography in 1954. Kinmonth succeeded in visualizing the peripheral lymph vessels by direct injection of water soluble contrast medium. By this technique it was not feasible to depict lymph nodes above the knee because of diffusion of medium to surrounding tissues. Lymphography is a technique that visualizes both lymph vessels and lymph nodes. This method is based on a combination of the two above-mentioned methods with injection of fat soluble contrast medium into peripheral lymph vessels. Lymphography was a very important examination which was used all over the world in the 1960s and 1970s. It has now been replaced by other examinations.

L22 ANSWER 8 OF 50 MEDLINE on STN DUPLICATE 5
2002007199. PubMed ID: 11248073. Intralymphatic immunization enhances DNA
vaccination. Maloy K J; Erdmann I; Basch V; Sierro S; Kramps T A;
Zinkernagel R M; Oehen S; Kundig T M. (Department of Dermatology, and
Institute of Experimental Immunology, Universitatsspital Zurich,
Schmelzbergstrasse 12, CH-8091 Zurich, Switzerland..
kevin.maloy@path.ox.ac.uk). Proceedings of the National Academy of
Sciences of the United States of America, (2001 Mar 13) 98 (6) 3299-303.
Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States.
Language: English.

Although DNA vaccines have been shown to elicit potent immune responses in animal models, initial clinical trials in humans have been disappointing, highlighting a need to optimize their immunogenicity. Naked DNA vaccines are usually administered either i.m. or intradermally. The current study shows that immunization with naked DNA by direct

injection into a peripheral lymph node
enhances immunogenicity by 100- to 1,000-fold, inducing strong and
biologically relevant CD8(+) cytotoxic T lymphocyte responses. Because
injection directly into a lymph node is a rapid and
easy procedure in humans, these results have important clinical
implications for DNA vaccination.

L22 ANSWER 9 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN 2001:504220 The Genuine Article (R) Number: 443QA. Safety and pharmacokinetics of naked plasmid DNA in the skin: Studies on dissemination and ectopic expression. Hengge U R (Reprint); Dexling B; Mirmohammadsadegh A. Univ Essen Gesamthsch, Dept Dermatol Venerol & Allergol, Hufelandstr 55, D-45122 Essen, Germany (Reprint); Univ Essen Gesamthsch, Dept Dermatol Venerol & Allergol, D-45122 Essen, Germany. JOURNAL OF INVESTIGATIVE DERMATOLOGY (JUN 2001) Vol. 116, No. 6, pp. 979-982. Publisher: BLACKWELL SCIENCE INC. 350 MAIN ST, MALDEN, MA 02148 USA. ISSN: 0022-202X. Pub. country: Germany. Language: English. \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

Gene therapy using naked DNA injected into muscle and skin is AB increasingly being used for vaccination and treatment purposes. Favorably, naked plasmid DNA does not exhibit the various limitations inherent to viral vectors, such as the elicitation of adverse immune responses and the risk of insertional mutagenesis. In order to assess the distribution and safety of naked plasmid  $\tilde{D}NA$  in a relevant animal model, we analyzed if intracutaneously injected plasmid DNA was transported to other organs and if ectopic expression occurred. When a "superdose" of a marker plasmid was injected intradermally, most organs were found transiently to contain the plasmid DNA for several days, whereas integration into the host genome was not detected. With the exception of ovary, however, mRNA expression only occurred in the skin, regional lymph nodes, and muscular tissues. From a safety standpoint, skin gene therapy with naked plasmid DNA can be considered safe due to the rapid biodegradation of plasmid DNA and the exclusive and transient expression of foreign genes in tissues known to take up DNA.

L22 ANSWER 10 OF 50 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN The Genuine Article (R) Number: 437LL. Rapid and wide-reaching 2001:459852 delivery of HIV-1 env DNA vaccine by intranasal administration. Tadokoro K; Koizumi Y; Miyagi Y; Kojima Y; Kawamoto S; Hamajima K; Okuda K (Reprint); Tanaka S; Onari K; Wahren B; Aoki I; Okuda K. Yokohama City Univ, Sch Med, Dept Bacteriol, Kanazawa Ku, 3-9 Fukuura, Yokohama, Kanagawa 2360004, Japan (Reprint); Yokohama City Univ, Sch Med, Dept Bacteriol, Kanazawa Ku, Yokohama, Kanagawa 2360004, Japan; Yokohama City Univ, Sch Med, Dept Internal Med, Yokohama, Kanagawa 2360004, Japan; Yokohama City Univ, Sch Med, Dept Pathol, Yokohama, Kanagawa 2360004, Japan; Tokyo Dent Coll, Dept Bacteriol, Mihama Ku, Masago, Japan; Yokohama Minami Kyosai Hosp, Dept Orthoped Surg, Yokohama, Kanagawa, Japan; Karolinska Inst, Swedish Inst Infect Dis Control, Stockholm, Sweden. VIRAL IMMUNOLOGY (5 MAY 2001) Vol. 14, No. 2, pp. 159-167. Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538 USA. ISSN: 0882-8245. Pub. country: Japan; Sweden. Language: English. \*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB

Although the potential of DNA vaccination is now beginning to be greatly appreciated, no detailed study of its localization in tissue or its expression kinetics has been reported. In this study, we investigated these issues using HIV-1 DNA plasmids administered either intranasally or intramuscularly, Fluorescence in situ hybridization (FISH) revealed that the human immunodeficiency virus (HIV) plasmids administered intranasally localized in the alveoli, lung, liver, spleen, regional lymph nodes, kidney, fetus, and esophagus, These HIV plasmids were detected 2 to 4 weeks after administration. We detected messenger RNA production of HIV env gene in the lung, liver and spleen, and human immunodeficiency virus type 1 (HIV-1)-specific proteins were detectable in the lung, These observations may provide important information for understanding the mechanisms of strong immune activation induced by DNA

vaccination via the intranasal route. This technology of DNA administration suggests possible practical applications for vaccination and probably for gene therapy.

DUPLICATE 6 L22 ANSWER 11 OF 50 MEDLINE on STN PubMed ID: 10467363. Distribution of retroviral vectors and 1999398752. vector producer cells using two routes of administration in rats. Kaloss M; Linscott M; Wey C; Lu P; Long Z; McGarrity G J; Otto E; Lyons R M. (Genetic Therapy, Inc, 938 Clopper Road, Gaithersburg, MD 20878, USA.) Gene therapy, (1999 Aug) 6 (8) 1389-96. Journal code: 9421525. ISSN: 0969-7128. Pub. country: ENGLAND: United Kingdom. Language: English. The clinical use of retroviral vector producer cells (VPCs) to deliver AB retroviral vectors efficiently to target cells has been investigated as a method to increase efficiency of gene delivery, presumably as a result of continued vector production in vivo. Studies were conducted in rats to evaluate the distribution of vector to distal organs and tissues as measured by transduction. Rats were treated with two doses of VPCs using two routes of administration: (1) subcutaneous injection, chosen to maximize both the dose and exposure of animals, thereby enabling identification of potential target organs under worst-case conditions; and (2) direct injection into brain parenchyma, chosen to mimic the intended clinical route of administration and provide an estimate of risk to patients receiving this therapy. Twelve organs or tissues were collected 7 days after administration of VPCs and analyzed by PCR for the presence of vector and vector producer cell sequences. Vector was detected most frequently at the site of injection by either route of administration. Less frequently, vector was detected in draining lymph nodes at the higher dose only using either route of injection. Single specimens of lung and contralateral skin were positive for vector following subcutaneous administration only. Vector was detected in gonadal tissue from a single low-dose male following subcutaneous administration, but this finding was not reproduced in any high-dose male or any males injected intracerebrally. In contrast, VPCs were detected only at the site of administration. The frequency of detection of VPCs 7 days after administration was higher when rats were injected by the intracerebral route. Based on these studies, gene transfer to distal organs or gonadal tissue following intracerebral administration of VPCs is not considered to be a risk to patients undergoing retroviral vector gene therapy for the treatment of brain cancer (glioblastoma multiforme; GBM).

L22 ANSWER 12 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000093020 EMBASE Lymphatic drainage of the heart and lungs in the pig: A preliminary study. Riquet M.; Hubsch J.P.; Chehab A.; Briere J.; Colomer S.; Hidden G.. Prof. M. Riquet, Laennec Hospital, Service de Chirurgie Thoracique, 42 rue de Sevres, 75007 Paris, France. riquet@lnc.ap-hop-paris.fr. European Journal of Lymphology and Related Problems 7/27 (80-84) 1999.

Refs: 17.

ISSN: 0778-5569. CODEN: EJLPE. Pub. Country: Belgium. Language: English.

Summary Language: English.

In anatomy and physiology the pig is remarkably like man and is therefore considered as Potential Organ Donor. It was then particularly interesting to reconsider the lymphatic drainage of both its heart and lungs (H.L)Fifteen dead pigs were studied. The technique comprised removal of the sternocostal shield and injection into the myocardium and/or beneath the visceral pleura of a colored mass that was supplemented by direct injection of the nodes revealed in that manner. First colored nodes were tracheobronchial located-under the tracheal carina (ITBN), above the left (LSBN) and right (RSBN) main bronchus, above the right upper lobe tracheal bronchus (TBN) - and located at the lower level of the cervical trachea (CMN). There was no other pretracheal neither pulmonary LN contrary to human. The lymphatic vessels (LV) of the heart connected with the LSBN, rarely with the CMN. The LV issuing from:

the ITBN connected with both the RSBN and LSBN and also with retrotracheal lymphcenter nodes (RTN); the RSBN connected with RTN, CMN or drained into the right jugulo subclavian venous confluent; The LSBN connected at times with RSBN and some lateroesophageal nodes, but generally drained into the left jugulosubclavian venous confluent, the arch of the thoracic duct (TD) and directly into the TD in the middle mediastinum, also an important lymph pathway in human. Lymphatics of the H.L. in pigs display anatomical patterns rarely observed in man but phylogeneticly explaining diseases as 'skipping' node metastases in lung cancer and chylothorax after heart and lungs surgery. In anatomy and physiology, the pig is remarkably like man. In 1966, Glauser underlined the advantages of Piglets as Experimental Animals in Pediatric Resarch : laboratory data comparing the newborn infant with the newborn piglet disclosed a striking similarity in the results reported for respiratory system. In adult research the pig's size proved to be a problem that was solved by breeding miniature pigs. Porcine coronary arteries have almost the same pattern as the human being and investigators have found the pig particularly valuable for the study of coronary arteriosclerosis. The similitude between the 2 species are so great and the differences so little that since recently pig is considered as a potential organ donor and most of its organs are thought suitable for xenotransplantation. In view of contributing to such major topics, it seemed particularly interesting to reconsider the lymphatic drainage of both heart and lungs in this species so closely related to human.

L22 ANSWER 13 OF 50 MEDLINE on STN DUPLICATE 7

1999068049. PubMed ID: 9851063. Three-dimensional and ultrastructural aspects of the lymphatic vascularization of the vermiform appendix. Azzali G. (Institute of Human Anatomy, Faculty of Medicine, University of Parma, Italy. anatnor@ipruniv.cce.unipr.it). Journal of submicroscopic cytology and pathology, (1998 Oct) 30 (4) 545-53. Journal code: 8804312. ISSN: 1122-9497. Pub. country: Italy. Language: English.

AB The aim of the study is to reveal the three-dimensional distribution and ultrastructure of the peripheral absorbing lymphatic vessels of the

vermiform appendix, since the gut-associated lymphoid tissue is necessary to the immune responses to the enteric antigens. Corrosion casts showed the beginning of the lymphatic vascularization at the tunica mucosa, which lacks intestinal villi, through a tight, delicate lymphatic network. This network drains the lymph by peculiar straight vessels, distributed in the mucosal beams that separate the adjacent follicle domes, in the fine network of the upper portion of the lymphatic basket, surrounding the lateral walls of the basal and medium portions of each lymphoid follicle. This network, which is made of large caliber vessels that are not dilated like sinuses, continues through small vessels into the large dome-like vessels of the submucosa, which in turn by way of the lymphatic vessels of the muscular tunica, drain into the subserous precollector valved lymphatic vessels that flow into the pre-lymph node collectors. We underlined that the particular fluidity of Neoprene latex and the direct injection method, when compared with other substances and injection methods, provided us with exceptionally clear and precise three-dimensional plastic images of the absorbing lymphatic vessels. Moreover, these images extraordinarily illustrated the preservation of the absorbing lymphatic spatial relationships with blood vessels. Ultrastructural features and three-dimensional models of ultrathin serial sections of the absorbing peripheral lymphatic vessels showed a continuous endothelial wall lacking basal lamina, as well as open junctions between adjacent cells. Moreover, we observed the presence of numerous lymphocytes, together with intense transendothelial migratory activity that occurs through intraendothelial channel formations, dynamic entities, at absorbing lymphatic vessels of the peri-interfollicular lymphoid tissue. Also, we saw that the germinal center, as well as the lymphoid follicle dome, lacked lymphatic absorbing vessels. In addition, many postcapillary high endothelial venules (HEV) were observed with lymphocyte migration into the extravasal compartment. Furthermore, we maintain that the absorbing peripheral lymphatic vessels (ALPA) of the tunica mucosa play an important role in liquid drainage. For the

peri-interfollicular vessels, we hypothesize a potential migratory and a reserve capacity for lymphocytes, as well as a conduction activity for the muscular tunica and submucosa vessels.

- L22 ANSWER 14 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN

  1997:464640 Document No. 127:175168 Deletion of alloantigen-reactive thymocytes as a mechanism of adult tolerance induction following intrathymic antigen administration. Jones, Nick D.; Fluck, Nick C.; Roelen, Dave L.; Mellor, Andrew L.; Morris, Peter J.; Wood, Kathryn J. (John Radcliffe Hospital, University Oxford, Oxford, OX3-9DU, UK). European Journal of Immunology, 27(7), 1591-1600 (English) 1997. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: Wiley-VCH.
- Direct injection of foreign antigen into the adult AB thymus is a potent route of antigen delivery for the induction of tolerance in vivo. It was demonstrated that tolerance to C57BL/10 (H2b/BL10) alloantigens can be induced in CBA/Ca (H2k/CBA) mice by intrathymic (IT) administration of BL10 spleen leukocytes coincident with transient peripheral immunomodulation of CD4+ T cells using a depleting anti-CD4 monoclonal antibody. T cell receptor (TCR) transgenic mice (BM3.6; H2k) expressing a CD8-independent TCR specific for H2Kb were used as recipients to facilitate investigation of the mechanisms responsible for tolerance induction by allowing visualization of events in the thymus following IT injection. IT administration of 5 + 107 BL10 spleen leukocytes and concomitant transient peripheral T cell depletion in BM3.6 mice resulted in a substantial H2Kb-specific deletion of transgenic-TCR+ (tg-TCR) thymocytes which was dependent on the level of tg-TCR expression. IT deletion and the failure to export CD8+ T cells to the peripheral lymphoid organs correlated with the induction of tolerance to H2Kb, TCR transgenic mice that had received IT injection of BL10 splenocytes and peripheral T cell depletion accepted a H2Kb+ cardiac allograft indefinitely. Anal. of tolerant BM3.6 mice revealed that there were low nos. of CD8+ T cells in the periphery giving rise to a substantially reduced reactivity in vitro despite the fact that no donor cells or IT deletion were observed in the thymi of the majority of tolerant mice. These results demonstrate for the first time that IT injection of foreign alloantigen into an adult thymus results in the deletion of thymocytes expressing a TCR specific for the injected alloantigen and suggest that this is an important mechanism of tolerance induction following IT injection of alloantigen in vivo. Anal. of tolerant TCR-transgenic mice suggests that IT deletion is not required for the maintenance of tolerance, and that peripheral mechanisms enforce continued hyporesponsiveness to H2Kb following transplantation.
- L22 ANSWER 15 OF 50 MEDLINE on STN DUPLICATE 8

  1998033894. PubMed ID: 9367025. Cytokines as an adjuvant to tumor vaccines: efficacy of local methods of delivery. Kurane S; Arca M T; Aruga A; Krinock R A; Krauss J C; Chang A E. (Division of Surgical Oncology, University of Michigan, Ann Arbor, USA.) Annals of surgical oncology: official journal of the Society of Surgical Oncology, (1997 Oct-Nov) 4 (7) 579-85. Journal code: 9420840. ISSN: 1068-9265. Pub. country: United States. Language: English.
- BACKGROUND: We examined alternative methods of delivering cytokines as an adjunct for priming lymph node (LN) cells draining sites of vaccine inoculation for the purpose of generating immune cells for adoptive immunotherapy. METHODS: Using syngeneic murine tumors we examined the ability of IL-2, IL-4, or GM-CSF delivered locally to a site of tumor inoculum to induce antitumor reactive draining LN cells. Mice were inoculated subcutaneously with tumor cells transduced to secrete cytokine; tumor cells admixed with fibroblasts transduced to secrete cytokine; or intralesional inoculation of cytokine in established tumor to induce sensitized LN cells capable of mediating tumor regression in adoptive transfer. RESULTS: Both IL-4 and GM-CSF cytokines were effective in enhancing the antitumor reactivity of vaccine-primed LN cells compared to IL-2, which was ineffective. The local delivery of GM-CSF by autocrine or paracrine secretion of genetically engineered cells, as well as direct

intratumoral delivery was capable of upregulating LN sensitization compared to systemic administration, which did not. CONCLUSIONS: The local delivery of GM-CSF as an adjuvant for tumor vaccination can be accomplished by various methods, including direct injection, which avoids the need for gene transfer.

DUPLICATE 9 MEDLINE on STN L22 ANSWER 16 OF 50 PubMed ID: 9267846. Use of the dog model for Duchenne muscular 97413203. dystrophy in gene therapy trials. Howell J M; Fletcher S; Kakulas B A; O'Hara M; Lochmuller H; Karpati G. (School of Veterinary Studies, Murdoch University, Perth, Australia. ) Neuromuscular disorders : NMD, (1997 Jul) 7 (5) 325-8. Journal code: 9111470. ISSN: 0960-8966. Pub. country: ENGLAND: United Kingdom. Language: English. Golden retriever muscular dystrophy (GRMD) is an excellent model for the AB study of the efficacy of gene therapy in dystrophin deficient myopathies for there are many similarities between affected dogs and Duchenne muscular dystrophy (DMD) in boys. GRMD is not caused by deletion mutation but results from a point mutation in the consensus splice acceptor in intron 6 of the canine dystrophin gene. As a result exon 7 is skipped during processing of the GRMD dystrophin messenger RNA. We have developed a rapid test which makes direct use of exon 7 specific genomic PCR products. We have undertaken preliminary experiments on gene therapy using the mini-gene and the full length gene alone and in combination with lipofectin and/or the bacterial beta-galactosidase reporter gene Lac Z. Following direct injection of the Lac Z plasmid, either alone or with lipofectin, about 50% of the sites showed expression

either alone or with lipofectin, about 50% of the sites showed expression when biopsied some 14 days later. The beta-galactosidase activity was present in muscle and granulation tissue but was never abundant. Pups injected intraperitoneally with Lac Z were found to have positive material in their mesenteric lymph nodes, liver and spleen. Those injected with Lac Z and lipofectin also had positive material in the

diaphragm, intercostal muscles and abdominal muscles, but again only a small amount of positive material was present at any of the sites. In animals directly injected into the muscle with the dystrophin mini-gene, half had positive staining for dystrophin in biopsies taken 14 days later. Of the 6 sites in the muscles of animals given the mini-gene and lipofectin only one had fibres positive for dystrophin when examined 14 days later. Six pups were injected directly with full-length gene construct and when biopsies were taken 10 days later two of the animals had strongly stained peripheries to a small number of fibres.

L22 ANSWER 17 OF 50 MEDLINE on STN DUPLICATE 10
97159158. PubMed ID: 9006499. A new immunocompetent murine model for oral
cancer. O'Malley B W Jr; Cope K A; Johnson C S; Schwartz M R. (Department
of Otolaryngology-Head and Neck Surgery, Johns Hopkins University,
Baltimore, Md, USA. ) Archives of otolaryngology-head & neck surgery,
(1997 Jan) 123 (1) 20-4. Journal code: 8603209. ISSN: 0886-4470. Pub.
country: United States. Language: English.

AB

OBJECTIVE: To develop and characterize a new immunocompetent murine model that attempts to parallel the clinical and biological nature of head and neck cancer. DESIGN: The growth rate and histologic characteristics of the SCC VII/SF cell line were initially determined in tissue culture experiments. Animal experiments were subsequently performed on C3H/HeJ mice. Using direct injection, 5 x 10(5) SCC VII/SF cells were delivered to the floor of the mouth of each animal. Animals were killed after 1, 2, and 3 weeks, and tumor growth, invasion, and regional and distant metastases were evaluated. RESULTS: Squamous cell carcinomas that could be palpated and measured externally were identified in the floor of the mouth of C3H/HeJ mice after 5 to 7 days. Local invasion into the mylohyoid musculature and mandible was present. Cervical lymph node and pulmonary metastases were identified between 2 and 3 weeks. CONCLUSIONS: This study introduces a new oral cancer animal model that shows initial locoregional tumor invasion, direct extension into the neck, early cervical metastases, and pulmonary metastases. These clinical and histopathologic attributes

reflect the biological behavior and tumor progression seen in human oral cancer and therefore provide a model for clinically applicable research for primary and metastatic head and neck cancer.

- L22 ANSWER 18 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 95288854 EMBASE Document No.: 1995288854. Locoregional immunotherapy Topics at the 13th and 14th meeting of the Japanese Research Society for Surgical Cancer Immunology. Amano S.; Kurosu Y.; Shibata M.. First Department of Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173, Japan. Biotherapy 9/7 (845-851) 1995. ISSN: 0914-2223. CODEN: BITPE. Pub. Country: Japan. Language: Japanese. Summary Language: English; Japanese.
- Seventy papers concerning locoregional immunotherapy were presented at the 1992.apprx.1993 meetings. The subjects were head and neck cancer, breast cancer, lung cancer, gastric cancer, liver cancer, colon cancer, metastatic cancer, peritonitis carcinomatosa and experimental animal tumors. The methods of administration of BRMs were direct injection into the tumor or the regional lymph nodes, or infusion into the hepatic artery or portal vein. Various BRMs were used (OK-432, PSK lentinan, IL-2, TNF, IFN-γ, and mono-clonal antibody, such as missile therapy). New and hopeful challenges have been launched to overcome cancer growth, using the new techniques developed in the field of molecular biology, for example.
- L22 ANSWER 19 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 95182130 EMBASE Document No.: 1995182130. Induction of cellular, but not humoral, tolerance to ovalbumin by direct injection into digestive tract segments or mesenteric lymph nodes in mice. Louis E.J.; Lamproye A.M.; Franchimont D.; Van Kemseke C.; Schaaf N.; Mahleu P.; Belaiche J.. Department of Gastroenterology, CHU of Liege, Domaine Universitaire du Sart Tilman,4000 Liege, Belgium. Regional Immunology 6/4 (251-256) 1994.

  ISSN: 0896-0623. CODEN: REGIE3. Pub. Country: United States. Language: English. Summary Language: English.
  - The mechanism of systemic tolerance induction after feeding a protein antigen is poorly understood. In particular, the functions of different segments of the digestive tract, the mucosa, and the mesenteric lymph nodes are poorly understood. Moreover, recent studies have shown phenotypical and functional differences between mucosal lymphocytes of the small bowel and the colon. We investigated the effect of preimmunization with ovalbumin, given orally or administered directly into different digestive tract segments or into the mesenteric lymph nodes, on the subsequent systemic immune response to this antigen. As with oral preimmunization, we found that these routes of preimmunization induced cellular systemic tolerance, but unlike oral preimmunization they did not induce humoral systemic tolerance. These results confirm induction of humoral and cellular tolerance after feeding a protein antigen; they also confirm that cellular and humoral tolerance may be dissociated under some circumstances. They further show that cellular systemic tolerance may be induced at different levels of the digestive tract, and that several steps may be involved in its induction by feeding a protein antigen. On the other hand, humoral systemic tolerance seems to be more specific for oral preimmunization, suggesting a role for intraluminal degradation or possibly for a particular timing of presentation of the antigen in this phenomenon. Finally, we failed to show a difference between the small bowel and the colon regarding the effect of local preimmunization with ovalbumin on the subsequent systemic immune response to this antigen, despite the functional and phenotypical differences recently described.
- L22 ANSWER 20 OF 50 MEDLINE on STN DUPLICATE 11
  94107863. PubMed ID: 8280708. A genetic approach to idiotypic vaccination.
  Hawkins R E; Winter G; Hamblin T J; Stevenson F K; Russell S J. (MRC

Laboratory of Molecular Biology and Centre for Protein Engineering, Cambridge, United Kingdom.) Journal of immunotherapy: official journal of the Society for Biological Therapy, (1993 Nov) 14 (4) 273-8. Journal code: 9102704. ISSN: 1053-8550. Pub. country: United States. Language: English.

Treatment of cancer with vaccines is an attractive prospect, but few AB tumours express suitable target antigens. With B-cell lymphomas, the idiotypic immunoglobulin (Ig) of the malignant B-cell should provide a suitable target but this requires a vaccine to be created for each patient. We propose a strategy for making such vaccines: first to clone the V genes of the idiotypic Ig, and second to inject the patient with the cloned DNA (genetic immunisation) in order to elicit an immune response against the encoded Ig. We have previously shown that the V genes of the idiotypic Ig can be identified from human lymph node biopsies by polymerase chain reaction amplification, cloning, and sequencing. In this report, we show that anti-idiotypic antibodies can be elicited by direct injection of an expression vector that encodes the V genes of murine antibodies (the V genes of B1.8, a murine hybridoma or of BCL1, a murine lymphoma line). This finding suggests a simple approach to the preparation of idiotypic vaccines for patients with B-cell lymphoma, which also circumvents the need for adjuvants.

L22 ANSWER 21 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN
1993:465 Document No. 118:465 Study on immune response of lymphocytes in the regional lymph nodes of gastric cancer by
 direct injection of active charcoal-adsorbed β
 (1→3) glucan. Shibata, Kazunari; Suzuki, Kazunobu; Tsurui,
 Shigeru; Tanifuji, Kiminori (Dep. Surg., Tokyo Med. Coll., Tokyo, Japan).
 Tokyo Ika Daigaku Zasshi, 50(3), 443-53 (Japanese) 1992. CODEN: TIDZAH.
 ISSN: 0040-8905.

Via an endoscope, active charcoal-adsorbed lentinan, lentinan, and active AB charcoal were locally applied to foci in 65 patients with curatively resectable gastric cancer before surgery, in an attempt to improve antitumoral activity of lymphocytes on the regional lymph nodes and to prevent malignant disease course progression. resulting immune response was then evaluated by determining the functions of lymph nodes by measuring the ratio of the composition of various T cell subgroups, IL-2 production, LAK cell activity, and NK cell activity. Lentinan reinforced with adsorptive active charcoal particles had superior high lymph specificity and exerted a slow-release effect by accumulating in the regional lymph nodes via the lymph flow. In addition, this type of lentinan proved more effective than locally or systemically applied lentinan for increasing the immunol. competence of group I lymph nodes and raising lymphocyte antitumoral activity. Thus, supplementing lentinan with adsorptive active charcoal particles and locally applying it may be effective for preventing tumor metastasis.

L22 ANSWER 22 OF 50 MEDLINE on STN
93143457. PubMed ID: 1843434. [Anatomy and topography of external iliac
lymph nodes in adults]. Anatomiia i topografiia
naruzhnykh podvzdoshnykh limfaticheskikh uzlov u vzroslogo cheloveka.
Shvetsov E V. Arkhiv anatomii, gistologii i embriologii, (1991 Jul-Aug)
100 (7-8) 50-7. Journal code: 0370603. ISSN: 0004-1947. Pub. country:
RUSSIA: Russian Federation. Language: Russian.

The investigation of the external iliac lymph nodes has been performed in 152 preparations of corpses of mature persons of both sex, who died from causes not connected with any disease of the lymphatic system, lower extremities and pelvic organs. The external iliac lymph nodes and their afferent and efferent lymphatic vessels have been revealed by means of interstitial injection of the lower extremities and pelvic organs, as well as by means of direct injection of Gerota mass into the lymphatic vessels. Form, amount, dimensions and topography of common iliac lymph

nodes have been studied. Lymphatic vessels, running from certain parts and organs of the body to various subgroups of the external iliac lymph nodes have been described, as well as efferent lymph vessels of these nodes. The external iliac lymph nodes are constant formations; the largest of them--lymph nodes of the lacuna--are nodes of the I step for the lower extremity lymph vessels. In 54% of cases in persons of both sex positive (right-sided) asymmetry has been revealed. Total amount of the iliac lymph nodes prevails in men, while their size is greater in women. The size of these nodes in persons of both sex is greater to the left than to the right. There are connections (in 3% of cases) between the external iliac lymph nodes and aortal and lumbar nodes of the opposite side.

- L22 ANSWER 23 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 1993:339492 Document No.: PREV199396036492. Anatomy and topography of external iliac lymph nodes in adults. Shvetsov, E. V.. Div. Anat. Human, I.M. Sechenov Mosc. Med. Acad., Moscow, Russia. Arkhiv Anatomii Gistologii i Embriologii, (1991) Vol. 100, No. 6-8, pp. 50-57. CODEN: AAGEAA. ISSN: 0004-1947. Language: Russian. The investigation of the external iliac lymph nodes AB has been performed in 152 preparations of corpses of mature persons of both sex, who died from causes not connected with any disease of the lymphatic system, lower extremities and pelvic organs. The external iliac lymph nodes and their afferent and efferent lymphatic vessels have been revealed by means of interstitial injection of the lower extremities and pelvic organs, as well as by means of direct injection of Gerota mass into the lymphatic vessels. Form, amount, dimensions and topography of common iliac lymph nodes have been studied. Lymphatic vessels, running from certain parts and organs of the body to various subgroups of the external iliac lymph nodes have been described, as well as efferent lymph vessels of these nodes. The external iliac lymph nodes are constant formations; the largest of them - lymph nodes of the lacuna - are nodes of the I step for the lower extremity lymph vessels. In 54% of cases in persons of both sex positive (right-sided) asymmetry has been revealed. Total amount of the iliac lymph r des prevails in men, while their size is greater in wome... The size of these nodes in persons of both sex is greater to the left than to the right. There are connections (in 3% of cases) between the external iliac lymph nodes and aortal and
- L22 ANSWER 24 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 12

lumbar nodes of the opposite side.

1989:430235 Document No.: PREV198988088493; BA88:88493. IMMUNOSUPPRESSIVE EFFECT OF A SMALL DOSE OF CYCLOSPORINE DIRECTLY INJECTED INTO THE THORACIC DUCT CO.BINED WITH SPLENECTOMY ON SURVIVAL OF RAT KIDNEY ALLOGRAFT. NAKAJI K [Reprent author]. SECOND DEP SURG, KYOTO PREFECTURAL UNIV MED. Journal of Kyoto Prefectural University of Medicine, (1989) Vol. 98, No. 7, pp. 745-754.

CODEN: KFIZAO. ISSN: 0023-6012. Language: JAPANESE.

Immunosuppressive effect of CsA directly injected into the thoracic duct, which had been ligated 3 days before, with or without splenectomy was examined in rat renal allograft model. Single injection of a small dose of CsA (4 mg/kg) into thoracic duct prolonged graft survival to 14.8 ± 4.6 days (n = 8) significantly, as compared with control group (9.3 ± 1.4 days, n = 9). Furthermore, combined treatment of direct injection of CsA into the thoracic duct and splenectomy yielded significantly longer graft survival to 22.9 ± 7.7 days (n = 7), as compared with CsA injection group (14.8 ± 4.6 days, p< 0.025) or splenectomy group (13.5 ± 4.1 days, <0.025). It is likely that this long graft survival was achieved due to suppression of activity of effector lymphocytes derived from the lymphnodes which kept in contact with selectively localized highly concentrated CsA in the thoracic duct,

and due to inhibition of cytotoxic antibody production by concomitant splenectomy. These results suggest that **direct** injection of CsA into the thoracic duct has a beneficial effect allowing a reduction in therapeutic CsA dosage and its side effects.

- L22 ANSWER 25 OF 50 MEDLINE on STN DUPLICATE 13
  89117359. PubMed ID: 3219074. [Individual and sexual characteristics of the common iliac lymph nodes in elderly persons].
  Individual nye i polovye osobennosti obshchikh podvzdoshnykh limfaticheskikh uzlov u liudei pozhologo vozratsa. Shvetsov E V. Arkhiv anatomii, gistologii i embriologii, (1988 Sep) 95 (9) 53-8. Journal code: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language: Russian.
- The common iliac lymph nodes (CILN) have been investigated on 24 preparations from corpses of elderly persons (5 male and 7 female corpses), died from the causes not connected with the lymphatic system diseases, lower extremities and pelvic organs. with their afferent and deferent lymphatic vessels are revealed by means of interstitial injection into the lower extremities and pelvic organs, as well as by means of direct injection into lymphatic vessels. The form, amount, size and topography of CILN are studied. Lymphatic vessels, running from certain parts of the body and organs to various subgroups of CILN are described, as well as lymphatic vessels, connecting the nodes both within each subgroup and between the subgroups. There is a tendency in prevalence of amount and size of the lateral subgroup of the lymph nodes over the nodes of other subgroups of CILN; tendency in prevalence of amount of the lymph nodes in men, and their size--in women; prevalence of amount of right CILN and their size in the left--in persons of both sex; in 70% of the cases the amount of afferent lymphatic vessels to CILN prevails over that of the deferent lymph nodes.
- L22 ANSWER 26 OF 50 MEDLINE on STN DUPLICATE 14
  88113762. PubMed ID: 3428927. Distribution of lung-associated lymphocytes from the caudal mediastinal lymph node: effect of antigen. Joel D D; Chanana A D. (Medical Department, Brookhaven National Laboratory, Upton, NY 11973. ) Immunology, (1987 Dec) 62 (4) 641-6.
  Journal code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United Kingdom. Language: English.
- Lymphocytes from the efferent lymph of the caudal mediastinal AB lymph node (CMLN) were labelled in vitro with 125I-iododeoxyuridine [125I] UdR and Na2(51) CrO4. The labelled cells were re-infused i.v. and their distribution in organs/tissues was determined 20-24 hr later. As indicated by tissue 125I-activity, pulmonary lymphoblasts had a marked tendency to relocate in the lung, regional pulmonary lymph nodes and spleen. Localization of efferent CMLN lymphoblasts was greater in antigenically stimulated segments compared to unstimulated segments of the lung. Dual antigen experiments indicated that the increased localization was not specific for the antigen which stimulated production of lymphoblasts used for in vitro labelling and reinfusion. Intranodal labelling of blasts by the direct injection of [1251] UdR supported the results obtained from in vitro labelling. In these studies, comparisons were made with the localization of lymphocytes obtained from thoracic duct lymph.
- L22 ANSWER 27 OF 50 MEDLINE on STN DUPLICATE 15
  88048928. PubMed ID: 3675209. [Anatomy and topography of the common iliac
  lymph rodus in human beings in the 1st period of
  maturity]. Anatomiia i topografiia obshchikh podvzdoshnykh
  limfaticheskikh uzlov u liudei pervogo perioda zrelogo vozrasta. Shvetsov
  E V. Arkhiv anatomii, gistologii i embriologii, (1987 Jul) 93 (7) 33-7.
  Journal code: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language:
  Russian.
- The invistigation of common iliac lymph nodes has been performed in 20 corpses of the first mature age of both sex (5 male and 5 female corpses) of persons died from causes not connected with the

lymphatic system diseases, the lower extremities and the pelvic organs. The common iliac lymph nodes with their afferent and efferent lymphatic vessels are revealed by means of interstitial injection into the lower extremities and the pelvic organs and with direct injection into the lymphatic vessels. The form, amount, size and topography of the common iliac lymphatic vessels have been studied. lymphatic vessels, that go from certain body parts and organs to various subgroups of the common iliac lymph nodes, as well as the lymphatic vessels that connect the nodes both within the subgroup and also between the subgroups. The amount and size of the lymphatic nodes of the lateral subgroup predominate over the nodes of other subgroups of the common iliac lymph nodes; the amount of the common iliac  $\mathbf{1}_{Y}$ -ph nodes predominates in men, and their size--in women. Amount of these nodes in the right and their size in the left predominate in both sex. Among the common iliac lymph nodes there are no teniform nodes, and efferent lymphatic vessels of the lateral and medial subgroup of the common iliac lymph nodes in 15% of cases run towards the lumbar nodes in the opposite side.

DUPLICATE 16 MEDLINE on STN L22 ANSWER 28 OF 50 PubMed ID: 3731379. The role of the Peyer's patch in 86272442. carcinogenesis. I. The adsorption from the gut and retention of 3-methylcholanthrene by Peyer's patches. Bost K L; Cuchens M A. Carcinogenesis, (1986 Aug) 7 (8) 1251-6. Journal code: 8008055. ISSN: 0143-3331. Pub. country: United States. Language: English. Radiotrader methods were used to determine the distribution of AΒ 3-methylcholanthrene (3-MC) within the lymphoid organs of rats following i.g. intubation, i.l. injection into the small intestine, i.v. injection or direct injection of the Peyer's patches with 3-[6-14C] methylcholanthrene (14C-MC). The data indicate that the gut-associated Peyer's patches and mesenteric lymph nodes were exposed to higher amounts of orally administered 14C-MC than an of the other lymphoid organs. Whereas the Peyer's patches exhibit if the highest sp. act. for longer periods of time when low amounts of 14C-32 were administered, the sp. act. of the mesenteric lymph node was greater when rats were intubated with higher amounts of 14C-MC. Furthermore, the Peyer's patches were exposed to higher amounts of possible metabolites of 14C-MC. Injection of 14C-MC into the small intestinal lumen resulted in increased ratios of the Peyer's patch sp. act. to mesenteric lymph node sp. act., indicating that by passing the stomach altered the distribution patterns. Data from rats in cted i.v. with 14C-MC demonstrated that mesenteric lymph nodes not Peyer's patches adsorbed and retained 14C-MC from the blook and indicated that the 14C-MC associated with Peyer's patches of i.g. to sted rats was adsorbed from the gut rather than from the blood. obtained from rats which were exposed to 3-MC by directly injecting Peyer's patches with 14C-MC also indicated that the Peyer's patch is were able to retain 3-MC once localized within this lymphoid organ, to metabolize the 3-MC and to possibly excrete the polycyclic aromatic hydrocarbon into the small intestine. Collectively the data indicate that Peyer's patches have an important role in the adsorption from the gut and subsequent retention of 3-MC and hence may be a likely target egan for lymphoid carcinogenesis following oral exposure to carcial enic polycyclic aromatic hydrocarbons.

L22 ANSWER 0 OF 50 MEDLINE on STN DUPLICATE 17
86105673. JubMed ID: 3943008. Salvage of stage IV intraoral squamous cell
carcine as with preoperative 5-fluorouracil. Ryan R F; Krementz E T;
Trues ale G L. Cancer, (1986 Feb 15) 57 (4) 699-705. Journal code:
03742 6. ISSN: 0008-543X. Pub. country: United States. Language: English.

AB A regimen for improving the salvage rate for Stage IV squamous cell
carcine a of the tongue, alveolar ridge and floor of mouth is presented.
This re hod utilizes pre-operative sensitization of the tumor and regional
lymph 4 as by the topical application of 5-fluorouracil

(5-FU) in the form of Efudex (Roche). The drug must be used topically at the tumos skin or tumor-mucous membrane interface to utilize the sensitiving properties of skin or mucous membrane. Further response is obtained by direct injections of 5-FU into the tumor. Later intravenous (IV) drip of 5-FU can be used particularly at the time of surgical resection. During the period of preparation until sensitized to 5-FU, patients must be restored to positive nitrogen balance and concurrent infections are controlled. Because of the importance of nutrition in restoring immunity, a feeding gastrostomy for these patients is recommended. The definitive surgery must include all bone that is involved, as 5-FU alone will not sterilize the bone. Of 15 patients who underwent the regimen outlined in this study, 12 of the patients with Stage IV intra-oral squamous cell carcinoma have had their primary tumor controlled for 17 months to 5 years at the time of this report.

L22 ANSWER 30 OF 50 MEDLINE on STN
87093952. PubMed ID: 3797998. Corrosion cast technique applied in
lymphatic pathways. Castenholz A. Scanning electron microscopy, (1986) (Pt
2) 599-605. Journal code: 0371617. ISSN: 0586-5581. Pub. country: United
States. Language: English.

- The paper deals with methods and results of the microcorrosion cast technique in lymph angiology. For the representation of the special organization of the lymph vascular system including the initial vascular structures, intranodal pathways, bigger collectors, and lymph trunks, the application of various injection techniques is necessary. The interstitial injection of Mercox proves to be suitable to show the initial lymphatics and prelymphatic spaces. Similarly, the intranodal injection makes visible the system of the lymph sinuses and the spaces of the reticular tissue in this organ. Casts of bigger collecting vessels, lymph trunks, and thoracic duct can be obtained by direct injection of the resin into the vascular lumen. Thus, these techniques enable to make visible the structural details of the cast preparations of all parts of the lymphatic system.
- L22 ANSWER 31 OF 50 MEDLINE on STN
  84178034. PubMed ID: 6712496. [Anatomy and topography of the lymphatic vessels and regional lymph nodes of the rectum in newborn infants and children to 3 years of age]. Anatomiia i topografiia limfaticheskikh sosudov i regionarnykh limfaticheskikh uzlov priamoi kishki u novorozhdennykh i detei do 3 let zhizni. Abdykerimov S A. Arkhiv anatomii, gistologii i embriologii, (1984 Feb) 86 (2) 65-9. Journal code: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language: Russian.
- In 30 corpses of newborns and children up to 3 years of age, by means of AB the intratissue and direct injection of the modified Gerota's mass, certain increase in number and size of the superficial inquinal lymph vessels belonging to the superior-medial group, as well as the pararectal and superior rectal lymph nodes has been noted. The diameter of both afferent and efferent lymphatic vessels in the nodes mentioned in children of 1-3 years of age is greater than in the newborns. The number of the afferent vessels running towards these nodes in most cases, regardless the age, prevail over the efferent ones, and the diameter of the latter is greater than in the afferent vessels. The pararectal lymph nodes in 80% of cases are the nodes of the first step for the lymph flowing from the rectum, in 15% the nodes of the first and second steps, simultaneously, and in 5% - of the third and fourth steps. The superior pararectal lymph nodes in 80% of cases are the nodes of the third and fourth steps, and i 20% of cases - those of the first and second steps for the lymph flowing from the rectum.
- L22 ANSWER 32 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN

  1984:79567 Document No. 100:79567 Experimental study of local chemotherapy with topical injection of adriamycin. Muto, Fumitaka (1st Dep. Surg., Kyoto refect. Univ. Med., Kyoto, Japan). Kyoto-furitsu Ika Daigaku Zasshi, 92(12), 2027-36 (Japanese) 1983. CODEN: KFIZAO. ISSN: 0023-6012.

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AB Local application of adriamycin [23214-92-8] is more efficient than i.v.
      injection in controlling lymph node metastasis and
      minimizing toxic side effects. This was demonstrated by injecting the
      drug into rat gastric mucosa and showing a high concentration of the drug in
 the
      stomach for a prolonged period with little toxic effect on the stomach.
      The concentration of adriamycin in the liver was considerably less than that
      observed after i.v. injection. In rats bearing AH-130 tumor in the foot pad,
      direction of adriamycin into the tumor increased
      the survival rate and had a greater efficacy than did the i.v. injection.
 L22 ANSWER 33 OF 50
                         MEDLINE on STN
                                                        DUPLICATE 18
 83121323.
            PubMed ID: 6218666.
                                  T cell help in cytotoxic T lymphocyte
     responses. Role of the I region in helper cell induction. Livnat S; Corley
     R B. Samsplantation, (1983 Jan) 35 (1) 78-83. Journal code: 0132144.
     ISSN: 041-1337. Pub. country: United States. Language: English.
AB
     We have studied the in vivo induction of T helper (TH) cells that
     parti. Wate in the generation of cytotoxic T (TC) lymphocytes. Helper
     actively was measured by the ability of the cells to help resting thymic
     TC cell precursors develop into effector TC cells in vitro.
     Direc injection of allogeneic spleen cells into the
     footpals of mice led to the generation of alloantigen-specific helper
     cells a the draining popliteal lymph nodes within 4
     to 6 d ws. Helper activity was mediated by nylon-wool-nonadherent Lyt-1+
     T lym: cytes; some activity was associated with Lyt-1,2+ cells. The
             requirements for both the induction and restimulation of C3H
     anti-: Od TH cells were investigated using cells from H-2k/H-2d
     recom' mant mice as in vivo immunogens and in vitro stimulators. Evidence
     is pr thred that shows in a direct assay that TH cells themselves are
     speci ... for I region-coded determinants. Thus, disparity at the left
     side the H-2 complex (K to I-E) but not at H-2K alone was necessary and
     sufficient to induce and reactivate TH cells. Proliferation in mixed
     lymph tyte culture was measured in combinations in which TH cells were not
     detec ble, supporting the idea that proliferation cannot be strictly
     consi red a measurement of helper cells.
L22 ANSWE OF 50
                        MEDLINE on STN
                                                       DUPLICATE 19
            FubMed ID: 7115115. [Anatomy and topography of human
82283346.
     bronc' memonary lymph nodes]. Anatomiia i
     topog
             iia bronkholegochnykh limfaticheskikh uzlov u cheloveka. Aubakirov
             My anatomii, gistologii i embriologii, (1982 Jun) 82 (6) 84-7.
            ande: 0370603. ISSN: 0004-1947. Pub. country: USSR. Language:
     Journ :
     Russi
             topses of persons at the age 17-76 years (28 men and 20 women)
AB
     In 48
            and topography of the bronchopulmonary lymph
     anato
            e been described. The nodes studies have been revealed
     nodes
     by me of interstitial and direct injection of
             as into the pulmonary tissues and lymphatic vessels with a
     Gerot.
     subsect in macro- and micropreparation of the lymph
            finites the bronchopulmonary lymph node
     nodes
            s described previously (posterior, inferior, anterior, superior),
     left &
             right interlobular bronchopulmonary lymph nodes
              revealed situating in the angles where the lobular bronchi
               the left and right main bronchi, as well as on surfaces of the
     lobul : bronchi turned towards the interlobular fissures. The left
     inter bular and upper bronchopulmonary lymph nodes
     are t
            st frequent occurrence. The left and right superior
    bronc
             Imonary lymph nodes occur in a greater number
     than :
               with nodes in other subgroups. The size of
            pulmonary lymph nodes varies within a wide
     the b
           form of the nodes depends on the place of their localization.
    range.
L22 ANSWE 5 6 5 50
                        MEDLINE on STN
                                                       DUPLICATE 20
83021796.
            Med ID: 7125916. [Variants in the number and size and the
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of the lumbar lymph nodes in the regional

```
of the liver in the human adult]. Varianty kolichestva, razmerov i
     topografiia regionarnykh dlia pecheni poiasnichnykh limfaticheskikh uzlov
     u vzreslogo cheloveka. Usovich A K; Borziak E I. Arkhiv anatomii,
    qistol dii i embriologii, (1982 Jul) 83 (7) 29-33. Journal code: 0370603.
     ISSN: John 1947. Pub. country: USSR. Language: Russian.
    By means of interstitial and direct injections of the
AB
     lymphallo bed of the liver and gall bladder, their regional lymph
     nodes from the lumbar group have been studied in 63 corpses of
     mature persons of both sex. The hepatic lymph vessels flow into the
     lumban apogh nodes in 73% of cases. Only the
     postacutal nodes (situating behind the abdominal part of the aorta) do not
     take the hepatic lymph nodes. The number of the
     hepatic regional lumbar lymph nodes varies from 1 to
     6, an their size is within the limits 2X2--30X10 mm. In 13% of cases
     intercological lumbar lymph nodes have been revealed
     (6X4 this in size), they are situated along the pathway of the visceral
     surface of the lymph vessels (of the right hepatic lobe) running towards
     large la ermediate lumbar lymph nodes.
                                                        DUPLICATE 21
L22 ANSWER 36 OF 50
                        MEDLINE on STN
            PubMed ID: 6795108. In vivo labelling of the spleen and
82051808.
     mesentaric lymph nodes with fluorescein isothiocyanate
     for I placyte migration studies. Pabst R; Binns R M. Immunology, (1981
           1 (2) 321-9. Journal code: 0374672. ISSN: 0019-2805. Pub. country:
     ENGLAND whited Kingdom. Language: English.
     Lymphic; in normal young pigs were labelled in vivo with fluorescein isothio mate in the spleen using an extracorporeal perfusion system and
     in meso dric lymph nodes by direct
             into the nodes. Labelled lymphocytes leave the spleen
           h rate via the splenic vein and migrate to different lymphoid
     organ . Emigrants from mesenteric lymph nodes left
     the notes slowly and revealed a different homing pattern. Evidence
             thed that a considerable number of lymphocytes from the parenchyma
            nodes via the vein and not by the classical route of
     leave
             thing lymphocytes via the efferent lymphatics. Fluorescein
     labelli tof lymphocytes in their normal micro-environment is a suitable
     method for lymphocyte migration studies.
                                                        DUPLICATE 22
L22 ANSWER 7 OF 50
                        MEDLINE on STN
             TubMed ID: 7416982. [Anatomy and topography of adult human
81020592.
     meser la lymph nodes]. Anatomiia i topografiia
             wykh limfaticheskikh uzlov vzroslogo cheloveka. Sapin M R;
     bryzł
             II; Makhmudov Z A. Arkhiv anatomii, gistologii i embriologii,
     Borzi
              78 (4) 60-4. Journal code: 0370603. ISSN: 0004-1947. Pub.
     (1980
             SR. Language: Russian.
     count
              number and age changes of the mesenteric lymph
     Topog
AΒ
              small intestine have been studied in 40 corpses of
     node:
               the age of 21-90 years. The mesenteric lymph
     node . Lair afferent and deferent vessels have been revealed by
             l of intersticial injection of coloured masses into the small
     the L
     inter to wall, as well as by a direct injection of
              nodes studied in the mesentery. Variability
     the :
            tal number of the mesenteric lymph nodes has
     in t
              istrated; topographic borders of separate groups of the
     been
             ymph nodes have been stated; topography of
     mese:
            rodes as regards the mesenteric blood
     the I
               been described. Quantitative changes (total and group) in the
     vess∈
               tymph nodes with age in grown-up persons
     mese
              emonstrated.
     have
                                                       DUPLICATE 23
L22 ANSWER OF 50
                        MEDLINE on STN
             nbMed ID: 435101. [Anatomical variants of the lymphatic vessels
79165172.
             g the inguinal lymph nodes]. Varianty
     conn
     anate limfaticheskikh sosudov, soediniaiushchikh pakhovye
             skie uzly. Shvetsov E V; Sapin M R. Arkhiv anatomii, gistologii
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i embriologii, (1979 Mar) 76 (3) 51-7. Journal code: 0370603. ISSN: 0004-1007. Pub. country: USSR. Language: Russian.

The str / of anatomical variants of lymphatic vessels connecting inguinal lymph n is was carried out on 56 corpses of adult persons if both sex whose deaths were not connected with lesions in the lymphatic system of the pelvis and lower extremities. The inguinal lymph noise and their afferent and efferent lymphatic vessels were detected by the method of intradermal injection and by the method of direct injection into the lymphatic vessels. It was stated that groups of the inguinal lymph nodes, as well is the nodes in every group determined, can serve as nodes of different stages for afferent lymphatic vessels running from different parts of the body and organs.

- L22 ANSWER 3 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 78302393 EMCLSE Document No.: 1978302393. Visualization of paravesical lymphatics by direct injection of contrast medium.
  Fiorelli C.; Lunghi F.; Nicita G.; et al.. Dept. Urol., Univ. Florence, Italy. Upology 11/2 (200-202) 1978.
  CODEN: U GYAZ. Pub. Country: United States. Language: English.
- AB Several ontrast media were injected endoscopically into the bladder of 10 patients. Satisfactory visualization of the paravesical lymphatics occurred in some cases. This was due to the physical properties of iodine compour and their degree of lymphatic absorption.
- L22 ANSWER 4 OF 50 MEDLINE on STN DUPLICATE 24
  77097326. Simed ID: 189098. Testicular lymphography: clinical study.
  Gandhi M G. Journal of urology, (1977 Feb) 117 (2) 174. Journal code:
  0376374. TSSN: 0022-5347. Pub. country: United States. Language: English.
- AB Direct : Stion of lipiodol into the parenchyma of the hum testis to study retroperitoneal lymphatics and lymph nodes is a potentially dangerous investigation. The information obtaine with this study is incomplete and far inferior when compared to result stained with standard procedures, such as pedal lymphography or cannulation of testicular lymphatics.
- L22 ANSWER 30 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
- 78048302 EMP To Document No.: 1978048302. Testicular lymphography: clinical study. C the Gandhi M.. Governm. Gen. Hosp., Gulbarga, India. Journal of Urology 117/2 (174) 1977.

  CODEN: CAAA. Language: English.
- AB Direct diction of lipiodol into the parenchyma of the hub testis to study retroperitoneal lymphatics and lymph nodes in potentially dangerous investigation. The information obtain with this study is incomplete and far inferior when compared to results obtained with standard procedures, such as pedal lymphography or cannula ica of testicular lymphatics.
- AB Lymple's modes on the anterior surface of the femur, in the region of the femore triangle were studied in 56 corpses of humans of either sex from 31 to 3 mars of age, dead of accidental causes or of diseases not related a lymphatic nodes. The investigation was carried on by the method or interstitial and direct injection of the Gerotal's as to some regions of foot skin, external genitalia and the skin of the anterior wall of the abdomen. It has been established that the sin of inguinal lymphatic nodes (both superficial and profound) in

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humans of either sex, are in direct dependence on the age of the person.
            t of inguinal lymphatic nodes in young people prevails over that
             ople. The external diameter of the afferent and efferent vessels
    in olu
             y humans is greater than in young ones. The amount of afferent
    in elde
             vessels to inguinal lymphatic nodes in most cases prevails over
    lymphat
            of efferent ones, independent of age and sex. The external
    diameter of the former is greater than that of the latter.
            OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
L22 ANSWER
    on STN
74210138 EN SE Document No.: 1974210138. [Lymph nodes
             latics of the pelvis and the pelvic limb of the goat]. DIE
    and ly
             FEN UND LYMPHGEFASSE DES BECKENS UND DER BECKENGLIEDMASSE DER
    LYMPH
    ZIEG ... DOS H.; Frewein J.. Inst. Makrosk. Anat. Tiere, Univ. Munchen,
             BERL.MUNCH.TIERARZTL.WSCHR. 87/6 (101-105)
    Germ .
    CODE : INTAM. Language: German.
              nodes of the pelvis and the pelvic limb were
    The 1
             in 46 goats of different breeds and different ages. Many of the
    exami
             lymphatics were visualized by injection of a mixture of Indian
     afferc
            water or Indian ink and serum into the subcutis, into fascias,
     ink a
     tendon, tendon sheaths, joint capsules and ligaments. The efferent
     lympha is were filled by direct injection into the
             es. The following lymph nodes
             ys present: Ln. popliteus, Ln. ischiadicus, Ln. inguinalis
     are :
            cialis, Ln. subiliacus, Lnn. iliaci mediales, and Ln. sacralis. Not
     supe
     alwa present are: Ln. tuberalis Ln. inguinalis profundus, and Ln.
    hypo tricus.
L22 ANSWER 44 OF 50 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
     on S
            BASE Document No.: 1974124958. Direct and indirect plaque forming
74124958
           a extrapulmonary lymphoid tissue following local vs systemic
     celle
            on of soluble antigen. Nash D.R.. East Texas Chest Hosp., Tyler,
            701, United States. Cellular Immunology 9/2 (234-241)
     Tex.
            CLIMB8. Language: English.
     CODI
            ain mice were immunized with solubilized SRBC stroma either by
     AKR
            injection into the lower respiratory tract or
     dire
     intro nously via the tail vein. The number of plaque forming cells (PFC)
     in the draining pulmonary lymph node (tracheobronchial
            nd spleen were determined by direct (IgM) and indirect (IgG(1),
     node)
            , IgA) plaque assays. Intravenously administered antigen induced an
     IgG(:
            ly strong IgM response in the spleen which was subsequently
     init:
            d by antibody of the IgG(1), IgG(2b), and IgA classes of
     foll
            lobulins. The tracheobronchial lymph node
     imm
            ed a minimal number of PFC representing all 4 types of
     cont
            lobulins studied. Conversely, following a single local injection of
     immu
           t directly into the lower respiratory tract, the tracheobronchial
     anti
           sponded with relatively high concentrations of PFC of all classes.
     node
            ponse in the spleen, although higher than background, was barely
     The :
            ble. The splenic response to locally administered antigen was,
            , considerably augmented as a result of a second local injection
     howe
            5 days after the initial stimulation. Under these conditions,
     give'
           . IgG(2b), and IgA were represented in both tissue sites by sharp
     IqG(
            es in the number and a decrease in the time of appearance of their
     incr
            ive antibody forming cells. Comparable changes were not noted for
     res
            e of IgM. Serum hemagglutination titers following a single
     the
            on by either route did not vary significantly during the time
     ini\epsilon
            of the experiment (28 days). The sera from locally immunized mice
     cour
            eated with the reducing agent dithiothreitol and hemagglutination
     were
            before and after treatment, were compared. The major serum
     tite
            y observed during the first 10 days following injection was
     acti
            d by reduction and could therefore by assigned to high molecular
     {\sf aff}e
            antibody (19S, 13S). Subsequent titers (days 13-26) were less
     weic
            ible to DTT and are considered to represent low molecular weight
     susc
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AB

AΒ

lobulins (7S).

immu

L22 ANSWER 45 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN 1969:489536 Document No. 71:89536 Two rapidly labeled RNA species in the polysomes of antibody-producing lymphoid tissue. Kuechler, Ernst; Rich, Alexander (Massachusetts Inst. of Technol., Cambridge, MA, USA). Proceedings of the National Academy of Sciences of the United States of America, 63(2), 520-7 (English) 1969. CODEN: PNASA6. ISSN: 0027-8424. Popliteal lymph nodes of rabbits stimulated to produce AΒ antibodies were pulse labeled in vivo by direct injection of uridine-3H. RNA was then extracted from isolated polysomes and single ribosomes. Fractionation of this RNA by polyacrylamide-gel electrophoresis revealed the synthesis of 2 discrete peaks of labeled RNA migrating in the region between 18 S ribosomal and 4 S transfer RNA. These peaks were found in the RNA extracted from polysomes but were absent from single ribosomes. When the polysomes were disrupted by FDTA treatment the RNA species no longer appeared as rapidly sedimenting material. These 2 RNA's have mol. wts. near 2.2 + 105 and 3.7 + 105 daltons. The chemical and biol. properties of these species as well as the mol. wts. were consistent with those expected for monocistronic messenger RNA coding for the antibody L and H chains, resp. L22 ANSWER 46 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN Document No. 69:50566 The production of high-titer antibody 1968:450556 against free angiotensin II. Boyd, G. W.; Peart, W. S. (Med. Sch., St. Mary s Hosp., London, UK). Lancet, II(7560), 129-33 (English) 1968. CODEM: LANCAO. ISSN: 0140-6736. A mader difficulty in radioimmunoassay of small polypeptide hormones was AB the levelopment of a suitable antibody. Most current techniques involve immuniting with peptide which has been chemical linked to a carrier protein. In the present study, specific antibodies to free angiotensin II were produced in high titer by immunization with angiotensin amide (hypertensin) which was adsorbed phys. onto microparticles of C. direct injection of the immunizing mixture into lym in nodes and spleen probably was more effective in antibody production than i.m. or i.p. injection in rabbits. Regardless of the soute of immunization, immune plasma or  $\gamma$ -globulin demonstrated a conscity to neutralize the biol. activity of angiotensin II extremely by and effectively. The technique of adsorption of antigen on C may mat utility in the preparation of antibodies to other small peptides of bio terest. Based on the antibody, a sensitive angiotensin say was developed. 27 references. L22 ANSWER 47 OF 50 MEDLINE on STN 68353299. Pubmed ID: 5664401. Evaluation of the direct inj ction of antigen into a peripheral lymph not for the production of humoral and cell-mediated immunity in the guinea-pig. Horne C H; White R G. Immunology, (1968 Jul) 15 (1) 65-74. code: 0374672. ISSN: 0019-2805. Pub. country: ENGLAND: United ı. Language: English. Kin L22 ANS 48 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN Document No. 61:13803 Original Reference No. 61:2326g-h 1964:413 Dira i injection of the thymus with antigenic sub rances. Sherman, Joseph D.; Adner, Marvin M.; Dameshek, William (Tt. 9 Univ., Boston, MA). Proceedings of the Society for Experimental Bic by and Medicine, 115(12), 866-70 (Unavailable) 1964. CODEN: PSEBAA. 137-9727. Dir it injuction of the thymus gland of the adult AB han her with a variety of substances (named), mostly of mammalian origin, pro ed charges in lymphoid tissues, bone marrow, and blood that ted thymic stimulation. The changes produced include splenomegaly, se of bone marrow lymphocytes, increase of  $\gamma$ -globulin, pos. Coc antiglobulin test, development of follicles within the thymus glana cell development within the thymus, spleen and lymph anemia, possibly of the autoimmune type.

L22 ANSWER 49 OF 50 CAPLUS COPYRIGHT 2004 ACS on STN 1949:15666 Document No. 43:15666 Original Reference No. 43:3095b-e The development of tumors in various tissues in mice following direct application of a carcinogenic hydrocarbon. Rask-Nielsen, Ragna Acta Path. Microbiol. Scand., Suppl., 78, 1-144 (Unavailable) 1948. Direct injection of a small amount of AB 9,10-dimethyl-1,2-benzanthracene into various organs of mice indicates that the thymus gland and lung are more susceptible than any of the other tissues which produce tumors spontaneously (subcutaneous tissue, skin, mammary tissue). Direct injection of large doses of this carcinogen into various organs induced tumors in thymus gland, lung, and also subcutaneous tissue but not in the other tissues capable of spont angous tumor formation, or in those not capable of spontaneous tumor formation (lymph nodes, spleen, bone marrow, kidney and testis) with the exception of one testicular sarcoma. Nonlocal tumor formation was observed in thymus gland and lung, with leukemic infilter tion only, in lymph nodes and spleen. Carcin panic agents do not produce tumors in tissues incapable of the sponta: ous generation of tumors. L22 ANSWER 50 OF 50 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 1995:345903 Document No.: PREV199598360202. Induction of cellular, but not humorsl, tolerance to ovalbumin by direct injection into di estive tract segments or mesenteric lymph nodes in mice. Louis, Edouard J. [Reprint author]; Lamproye, Annouk M.; Franchiment, Denis; Van Kemseke, Catherine; Schaaf, Nicole; Mahieu, Philipper Pelaiche, Jacques. Dep. Gastroenterol. Immunol, CHU Liege, Domaine Thiv. du Sart Tilman, 4000 Liege, Belgium. Regional Immunology, (1994 (195)) Vol. 6, No. 4, pp. 251-256. ISSN: (%6-0623. Language: English. The mechanism of systemic tolerance induction after feeding a protein AB antigen is poorly understood. In particular, the functions of different segment of the digestive tract, the mucosa, and the mesenteric are poorly understood. Moreover, recent The shown phenotypical and functional differences between mucosal lymphocour of the small bowel and the colon. We investigated the effect re ization with ovalbumin, given orally or administered directly of prei ant digestive tract segments or into the mesenteric into de , on the subsequent systemic immune response lymph atigen. As with oral preimmunization, we found that these routes to this unization induced cellular systemic tolerance, but unlike oral of  $\mathtt{pr}\epsilon$ preimme zation they did not induce humoral systemic tolerance. These result and induction of humoral and cellular tolerance after feeding a prot entigen; they also confirm that cellular and humoral tolerance strociated under some circumstances. They further show that may ¹ stemic tolerance may be induced at different levels of the cell . fract, and that several steps may be involved in its induction dige: rotein antigen. On the other hand, humoral systemic by f∈ toler seems to be more specific for oral preimmunization, suggesting a role i ntroluminal degradation or possibly for a particular timing of on of the antigen in this phenomenon. Finally, we failed to present Iference between the small bowel and the colon regarding the show a local preimmunization with ovalbumin on the subsequent systemic **ef**fec: immun " sponse to this antigen, despite the functional and phenotypical es recently described. diff∈ => s antical resentation TYTIGEN PRESENTATION T<sub>1</sub>23 => s 123 an andritic cell Las AND DENDRITIC CELL L24

=> s 124 as 'ytotoxic response

=> s 125 and lymph node

L25 AND LYMPH NODE => dup remov 126 PROCESSING C PLETED FOR L26 4 DUP REMOVE L26 (2 DUPLICATES REMOVED) L27 => d 127 1-4 cbib abs L27 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN 2001:712021 Document No. 136:4679 Plasmid DNA encoding CCR7 ligands compensation for dysfunctional CD8+ T cell responses by effects on ells. Eo, Seong Kug; Kumaraguru, dendri Udayasa r; Rouse, Barry T. (Laboratory of Viral Immunology, Department of Mice clogy, University of Tennessee, Knoxville, TN, 37996, USA). Journal E Immunology, 167(7), 3592-3599 (English) 2001. CODEN: JOIMA3. ISSN: 0(2-1767. Publisher: American Association of Immunologists. Lymphotexin  $\alpha$ -deficient (LT $\alpha$ -/-) mice, which lack AB lymph r 'es and possess a disorganized spleen, develop dysfunctional CD8+ T cells upon HSV infection and readily succumb to ephalitis. Such mice do develop apparently normal cific CD8+ T cell responses, as measured by MHC class 1 taining, but the majority of cells fail to become cytotoxic or tide-induced IFN- $\gamma$  production In the present study, the onstrate that functional defects of CD8+ T cells in  $LT\alpha$ -/- reaction and largely rectified by the administration of plasmid MA encoding CCR7 ligands before HSV infection. Treated mutant mice de eloped increased peptide-specific cytotoxic responers, enhanced nos. of CD8+ T cells capable of producing IFN- $\gamma$ , we well as improved resistance to HSV challenge. The corrective effect of chemokine treatment appeared to result from improved ell-mediated Ag presentation. Thus, a major dendr of the treatment was an increase in splenic dendritic conse in CCR7 ligand-treated LT $\alpha$ -/- mice with such cell populations showing improved APC activity in vitro. Our **sp**lend ment that functional defects of CD8+ T cells can be corrected, and resul. as value of plasmid vector encoding appropriate chemokines to indi wh immunotherapy. L27 ANSWER - CP 4 CAPLUS COPYRIGHT 2004 ACS on STN cument No. 134:264700 Dendritic cell 2000:71768 by danger and antigen-specific T-cell signaling. McLellan, A. activ E.-B.; Kampgen, E. (Department of Dermatology, University of D.; B Wherzburg, 97080, Germany). Experimental Dermatology, 9(5), which 2000. CODEN: EXDEEY. ISSN: 0906-6705. Publisher: Wuerz 313-3 l ternational Publishers Ltd... Munks 199 refs. Recent transplantation, animal and in vitro A rev AΒ et a dependence of some immune reactions on tissue damage. studi factors involved in enhancing immune responses through Altho have yet to be identified, recent data suggests that one of tissv of these cellular stress factors is the bone marrow derived the t el (DC). DC are potent initiators of dendr mmune responses and hold the key to immune reactions through prima: they to sense changes in their local environment and respond their to induce T-cell immunity, or possibly tolerance. In the appro: TC are also influenced by antigen-specific lymph  ${\tt i} \in {\tt m} \ {\tt T}$  cells, which may extend and amplify DC antigen presenting **s**igna ie , especially for the stimulation of cytotoxic capal . It now appears that both tissue damage and reape antic - Securic T-cell derived signals act together on the DC to promote te immune reaction to antigen. Thus DC antigen presenting the a te immune reaction to antigen. Thus DC antigen presenting behave to only dependent on the context of antigen encounter in the perip' my, also on the availability of antigen-specific T cells and

their "-cell receptor specificities.

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L27 ANSWED 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
            Document No. 134:145994 Dendritic cell
2000:829825
     elimination as an assay of cytotoxic T lymphocyte activity in vivo.
     Ritchie, D. S.; Hermans, I. F.; Lumsden, J. M.; Scanga, C. B.; Roberts, J.
     M.; Y g, J.; Kemp, R. A.; Ronchese, F. (Malaghan Institute of Medical
     Resea h, Wollington School of Medicine, Wellington, N. Z.). Journal of
     Immune brical Methods, 246(1-2), 109-117 (English) 2000. CODEN: JIMMBG.
             2-1759. Publisher: Elsevier Science B.V..
     ISSN:
     We she an this paper that the survival of antigen-loaded
AB
     dendri ic calls in vivo may be used as a sensitive
     readow of CTL activity. We have previously shown that dendritic
     cells abeled with the fluorescent dye CFSE and injected
            meansly into mice migrate spontaneously to the draining
     sub-c.
               where they persist for several days. In the
     lymr 🗅
            of effector CTL responses, dendritic cells
     pres
            with specific antigen rapidly disappear from the draining
     load-
             'e. In this paper we extend the above
     lymp.
            done and set up a simple and sensitive method to reveal CTL
     obser
     activi
             in individual mice in vivo. Dendritic cells
            led with two different fluorochromes, loaded with antigen or left
     were
             4, and mixed together before injection into mice. We show that
     untre
            . Calleitic cells loaded with specific antigen
     only
     were a sared from the draining lymph node, while
                Als not loaded with antigen remained
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             et. Cytotoxic responses generated by
     unaí
             tion with peptide-loaded dendritic cells, or
     by into this with influenza virus, could be revealed using this method.
             n of the differential survival of dendritic
     celle and ions mixed together also allowed us to accurately
                disappearance of dendritic cells, irresp.
     evalı
             iffer in the injection site and other parameters. Given the
     of var
                 dritic cells to efficiently take up and
     abili
     pressi condition antigens, nucleic acids and apoptotic bodies, this method
     may allo allow the evaluation of cytotoxic activity against antigens that
            ah lasterized in terms of peptide epitopes.
             OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
L27 ANSWER
                                                        DUPLICATE 1
     on ST
             MARCH [Strategies developed by HIV for escaping immune response].
1999321139
              A I SCHAPPEMENT AU SYSTEME IMMUNITAIRE DU VIH. Benaroch P.; Le
     STRATE
                  maroch, Inserm U. 520, Institut Curie, Batiment Lhomond, 26
     Gall S
                  148 Paris Cedex 05, France. Medecine/Sciences 15/8-9
     rue d'
     (950-
                  19.
     Refs.
             67-(0)4. CODEN: MSMSE4. Pub. Country: France. Language: French.
     ISS1:
     Summer Lange ge: French; English.
            ction relies amazingly on dendritic cells (DC)
    HIV 🗔
AB
             , i ^{\circ} replication and its ability to escape the immune system. DC
     for k
             ial antigen presentation and possess
     are s
            ne lility to stimulate naive T cells. In periphery, DC are spread
     the u
            in . We mucosae where they represent the first cells that HIV can ficiently contribute in its spreading by migrating to
     in th
     infec
                   major site of infection. Infected DC can
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             . . tivated T cells to form syncitia that become fantastic
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            3 O. Wiral production. During the asymptomatic phase, follicular
     fact
            mph les trap HIV particles at their cell
    surfac . replimenting the major reservoir of HIV. Thus, CD4+ T cells
    become inferred by circulating through the dendritic network. HIV
            n mag impede DC capacity to present viral antigens and induce a
    infec
             in IC numbers. Importantly, disappearance of DC is linked to the
    decre
    estal . 'men' of AIDS. Therefore, DC are key players at the different
    steps - HIV infection. HIV particles incorporate several human
             traineding MHC class II molecules, when budding from infected
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cells. The role of these molecules is discussed in the light of recent results suggesting that they could be involved in the efficiency of virus entry is well as in neutralizing important components of the antiviral cellul r response. Antigen presentation by MHC class II mo cules might also be affected by the HIV infection. HIV has d a strategy to down regulate surface MHC class I molecules, which allow infected cells to escape the cytotoxic response . This 'own modulation is mediated by the Nef protein, the expression of which diffies the intracellular trafficking of MHC class I molecules. Recent osults suggest that Nef may connect them to the cellular machinery  $involv\epsilon$  in transport to endocytic compartments from the plasma membrane as well as from the Golgi apparatus. Through its very high genomic variability, LIV creates numerous substitutions amongst the sequences encodi q epitopes presented by MHC class I molecules and recognized by cytoto ic T cells. This may result in loss of presentation by MHC class I moler as, or in loss of T cell reactivity. => s metho! L28 1253. 4 METHOD => s 128 and inducing CTL response 13 L AND INDUCING CTL RESPONSE => dup remove 129 PROCESSI: 1 OMPL TED FOR L29 6 DUP REMOVE L29 (7 DUPLICATES REMOVED) => d 130 1- cbib abs L30 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 2003:130796 Document No.: PREV200300130796. Dendritic cell (DC) based therapy for cer ico cancer: Use of DC pulsed with tumour lysate and matured with a novel syn hatic clinically non-toxic double stranded RNA analogue poly (I):poly (C 30) (Ampligen(R)). Adams, M. [Reprint Author]; Navabi, H.; Jasani, B.; Man, S.; Fiander, A.; Evans, A. S.; Donninger, C.; Mason, M. Vel wie Nichtrust, Velindre Hospital, Whitchurch, Cardiff, CF 14 2TL, UK. mal adam evelindre-tr.wales.nhs.uk. Vaccine, (30 January 2003) Vol. 7-8, pp. 787-790. print. ISSN: 264-410X (ISSN print). Language: English. pilloma virus (HPV) found in 99.7% of cervical cancers represents ctive immunotherapeutic target for novel adjuvant dendritic cell an att in Therapy. DC primed with HPV antigens have been shown to be ing CTL responses powerful capabl cate established murine tumours expressing HPV16 antigen. enough ur lysate has been found to be an effective means of of. The III In tymour associated antigens in animal models and in pri is leading to significant anti-tumour responses. Autologous cli ed with somicated HPV expressing tumour lysate have been shown to sle of inducing HPV specific classes I and II T-cell immunity in a be c initial study. Synthetic double stranded polyribonucleotides are pil∈. e in vitro activation/maturation agents capable of inducing a eff stage La phenotype producing high levels of IL12. However, the sta demen poly (I):poly (G) has proved to be clinically toxic. pro is vitro data have demonstrated that a novel clinically Preli ocue polymer poly (I):poly (C12U) (Ampligen(R)) can nondice in vitro maturation of human monocyte derived DC with eff∈ utive IL12 production. Human monocyte derived DC primed sus ou sate and matured with synthetic dsRNA may therefore offer an wit: of optimising Th1 specific anti-cancer T-cell responses in B 1. ations. This strategy is currently being tested in a clinical cance

L30 ANSW 1016 FIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN 2001:3311 Hent No.: PREV200100331113. Immunization with a

a per first with cervical cancer.

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tumor-resociated CTL epitope plus a tumor-related or unrelated Th1 helper
               peptia was protective CTL immunity. Casares, Noelia; Lasarte, Juan
               Jose [ ] r :t author]; Lopez-Diaz de Cerio, Ascension; Sarobe, Pablo;
                                  et Melero, Ignacio; Prieto, Jesus; Borras-Cuesta, Francisco
               Ruiz,
               [Repri
                                            hor]. Departamento de Medicina Interna, Facultad de Medicina,
               Universide Mayarra, Irunlarrea 1, E-31008, Pamplona, Spain.
                               e@ ...v.es; fborras@unav.es. European Journal of Immunology, (June,
               jjlar
               2001) >>>1. 31, No. 6, pp. 1780-1789. print.
               CODEM: DJIMAF. ISSN: 0014-2980. Language: English.
               Immurization with cytotoxic T cell epitope SPSYVYHQF (AH1), derived from
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              MuLV bis envelope protein expressed by CT26 tumor cells, does not protect
              BALE / against challenge with CT26 tumor cells. By contrast,
                         with AH1 plus T helper peptides OVA(323-337) or SWM(106-118)

1 and Th0 profiles, protected 83% and 33% of mice,

Interestingly, immunization with AH1 plus both helper

or id the efficacy to 33%. We identified the endogenous T
               elici
               respon
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                                                   (320-333) from gp70 which elicits a Th1 profile and is
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                                As for OVA(323-337), immunization with p(320-333) attect against tumor challenge. However, p(320-333) plus
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               alone
               AH1 merget id 80% of mice at day 10 after vaccination. Only 20% of mice
                                    and with AH1+OVA(323-337) or AH1+p(320-333) were protected when
               vacci
               chall good and any after immunization. Treatment with OVA (323-337) or
              with round established tumors delayed tumor growth. Our remarks tumor-related as well as tumor-unrelated but strong Th1
              pey is a seful for inducing CTL re immunotherapy.
L30 AN TOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
              29 : No.: PREV200100291318. Protein sigmal-mediated DNA imagni to a nst HIV. Maj, Jerzy G. [Reprint author]; Hone, D. M.; Shata, ... I could, D. W. [Reprint author]. Veterinary Molecular
 2001:29
              Biolc M rand diate University, Bozeman, MT, 59717-3610, USA. FASEB
                                      d) 7, 2001) Vol. 15, No. 4, pp. A364. print.
               Journ
              Me-ti- nual Meeting of the Federation of American Societies for
                                                       bgy on Experimental Biology 2001. Orlando, Florida, USA.
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                        immunity, we have adapted M cell-directed DNA

the M cell ligand, protein sigmal from reovirus. We

tive froted protein sigmal receptor-positive cells with the

rate from sigmal and poly-L-lysine (PL) combined with plasmid
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             DN. I c regiments, groups of BALB/c mice were intranasally (i.n.) impurited a lateral and poly-B-Tysine (PL) mice were intranasally (i.n.) impurited a lateral and poly-B-Tysine (PL) mice were intranasally (i.n.) impurited a lateral and poly-B-Tysine (PL) mice were intranasally (i.n.) impurite deal and poly-B-Tysine (PL) proposed and poly-B-Tysine (
                                       the symphocytes from local and distal tissues were examined by a standard 51Cr release assay. Ex vivo lung, spleen formulated co160-immunized miss.
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200214586 TD: 11877044. Preliminary study on CTL enhancement
             inde b L. and modified HL-60 cells. Li C; Fu J. (Shenzhen Chill and Hc. 1997), Shenzhen 518026, China. ) Zhonghua xue ye xue za zhi = Zl ng xue (22 zazhi, (2001 Jan) 22 (1) 17-9. Journal code: 8212398.

ISSN: C 172, 1993. country: China. Language: Chinese.
             OBJEC De Lee the mechanism of enhancing killing activity of tumor
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cells through a troviral vector PL-IL-4-SN. Wild and IL-4 mTC were used
                                   to indude traponses, and cell surface molecules were assayed by flow
                                                                                                                        TSULTS: The killing activity of tumor cell-specific CTL in
                                   cytone av.
                                   IL-4 grant increased from 11.8% to 77.2%, about sevenfold higher than the decided by wild HL-60 cells (P < 0.01). High level expression
                                   of MH clar if antigens as well as B7-1 and ICAM-1 molecules was observed in IL- mT. The empression of MHC class I antigen was not affected by
                                   IL-4 g ne rodification. The expression of cell surface molecules induced
                                   by IL-4 mT was completely abrogated by anti-IL-4 McAb. A significant
                                    increase of The secretions was detected during IL-4 mTC inducing
                                  CTL response were
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430684. The 19759884. Controlled lipidation and encapsulation of pepti a proposed to mucosal immunizations. Mora A L; Tam J P. (Deparate approach to mucosal immunizations. Mora A L; Tam J P. (Deparate approach to mucosal immunizations. Mora A L; Tam J P. (Deparate approach to mucosal immunications. Mora A L; Tam J P. (Deparate approach to mucosal immunication, Mora A L; Tam J P. (Deparate approach to mucosal immunication) (Baltimore, Md.: 1950)
1951 (7) 3616-23. Journal code: 2985117R. ISSN: 002: 1975 (1) 4016-23. Journal code: 2985117R. ISSN: 002: 
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Kingsmin, Biotech Pharmaceuticals Ltd, Oxford, UK.)

Im uno de S. B. 87 (2) 171-8. Journal code: 0374672. ISSN:

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Unity: ENGLAND: United Kingdom. Language: English.

The inclusion scential component of protective immunity against vital justices for generating such responses in a unit be of great value in vaccine development. We de such a recombinant antigen-presentation system based on the december of vital component of vital components. We de such a recombinant antigen-presentation system based on the december of vital components of vital components. We december of vital components of vital components of vital components of vital components. We december of vital components of vital components of vital components of vital components of vital components. We december of vital components of vital com
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